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TUMOR OF TACTILE END ORGANS

JAN CAMMERMEYER
OSLO, NORWAY

THE OCCURRENCE of a tumor consisting of tactile end organs is rare. Foot,[1] in his review of tumors of the peripheral nerves in 1940, said about the end organs: "That there should be tumors of these is to be expected." Such a possibility has been confirmed in the present case in which a tumor was found which in its tinctorial properties and in its structure differs from those previously described as far as I am aware of them.

Thoma[2] in 1894 described a neuroma of a pacinian corpuscle, an observation referred to by Borst[3] in 1902 and by Ewing[4] in 1940. Most likely, also, Axman[3] observed hypertrophy of a similar organ. In a patient suffering from plexiform neurofibroma, Brøgli[5] demonstrated many small tumors of connective tissue with three to eight tactile corpuscles. The maximum length of these was 190 microns, with a maximum width of 100 microns. They were surrounded by one to three layers of connective tissue, which sometimes increased in number from ten to thirty. Some regions showed cancer of the fibromatous tissue. A nearly identical case was published by Scherer,[6] who found many polyhedral tactile corpuscles. These appeared as lamellated organs of folded tactile cells surrounded by a single layer of connective tissue. In the intracorpuscular cells the nuclei were situated peripherally. Many corpuscles were gathered in groups the size of a bean, attached to the main neurofibromatous tumor.

From the Institute of Pahtology (Prof. L. Kreyberg, M.D., director) and the Institute of Anatomy (Prof. K. E. Schreiner, M.D., director), University of Oslo.

1 Foot, N. C.: Arch. Path. **30**:772, 1940.

2. Thoma, cited by Brøgli,[5] Foot[1] and Scherer.[6]

3. Cited by Brøgli.[5]

4. Ewing, cited by Foot.[1]

5. Brøgli, M.: Frankfurt. Ztschr. f. Path. **41**:595, 1931.

6. Scherer, H. J.: Virchows Arch. f. path. Anat. **292**:479, 1934.

7. Masson, P.: (*a*) Lyon chir. **21**:257, 1924; (*b*) Ann. d'anat. path. **1**:3, 1924; (*c*) **3**:417 and 657, 1926; (*d*) Arch. per le sc. med. **50**:47, 1927; (*e*) Am. J. Path. **4**:181, 1928; (*f*) in Penfield,[22] vol. 3, p. 1095; (*g*) Bull. Soc. franç. de dermat. et syph. **42**:1112 and (*h*) 1278, 1935.

After the brilliant studies of Masson [7] during the last two decades, the relationship between many tumor types and tactile end organs has been confirmed. Studying the glomic tumor or the *glomus neuromyo-artériel* in the years 1924 to 1927, he demonstrated in it vessels, smooth muscles and nerve elements, such as cells of Schwann and epithelioid cells. He pointed out the similarity of structure between this type of tumor and the normal glomus in the subepidermal connective tissue. About the same time (1926) Masson observed in the nevus tumors a hyperplasia of the cells of Schwann which led to the formation of *lames folliacées* or Verocay bodies. These could be interpreted as folded lamellas of tactile cells in the Meissner bodies. The same tumor could also contain areas with a neoplastic reaction of the tactile disks of the epidermis. Masson [7g] mentioned that most likely the neurofibromatous tumor itself developed from cells of Schwann. In this tumor the cells may be able to differentiate into Verocay bodies and tactile end organs of Meissner.

REPORT OF A CASE

A man 50 years of age had, on the mediovolar side of his left second finger, a congenital tumor. The medial side of the two outer phalanges showed an oval protrusion. On the ulnar side of the tip of the same finger an exostosis was observed. The man could work without any difficulty and did not complain of any pains. In the last two to three years the tumor had grown somewhat larger. The whole tumor with the bone exostosis was completely removed by Dr. Herman G. Gade, temporary chief of Surgical Department A of the University Clinic, Oslo.

Dr. Gade gave me permission to use the clinical records.

There were no postoperative complications. On removal the tumor seemed to be a common perineural fibroma or neurofibroblastoma. The patient did not show traces of any other tumor, and inquiry disclosed no neurofibromatosis in his family.

When the tumor was examined in the Institute of Pathology, it appeared encapsulated, hard, fibromatous, whitish, with the total length 6 cm., the greatest width 3 cm. and the thickness 1.5 cm. The shape was oblong, and the surface showed many small rounded nodules, one of them longer than the others. On one side the tumor was attached to a small flat piece of bone.

Microscopic Examination.—Microscopic examination revealed masses of connective tissue. The tissue was looser at the periphery, with many large vessels and a pacinian corpuscle. In the central parts of the fibrous tissue were a few small nodules, which differed considerably in size. They showed a peculiar structure and were well delimited without any tendency to infiltrate the surrounding tissue. In the center of the tumor the connective tissue formed a rounded fibrous mass, whereas in the more peripheral parts it extended into many small processes, which were separated by fat, vessels and a loose connective tissue. In figure 1 individual nodules may be recognized surrounded by concentrically arranged, parallel collagenous fibrils. The breadth of this capsule-like structure is greatest in the largest nodules. Extending from the larger external capsule were fine septums of connective tissue which divided the nodules into smaller parts or fields and invaded them completely. Finally the collagenous fibrils enclosed the indi-

vidual small rounded and oval corpuscles which constituted the nodules of the tumor (fig. 2). Thus a striking similarity between these capsules, septums and whirls of connective tissue and the different sheaths of a peripheral nerve was disclosed (fig. 1).

The well delimited nodules were composed of small groups of oval, rounded or more irregularly shaped corpuscles (fig. 2). Peripherally in the corpuscles

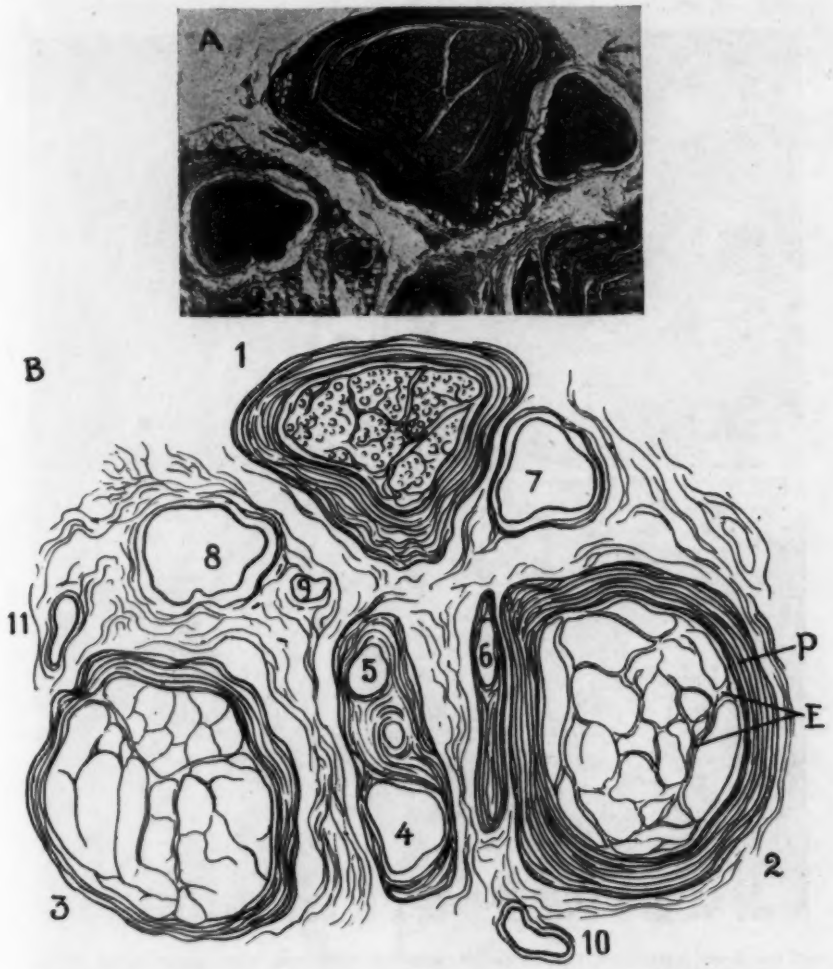

Fig. 1.—*A*, conglomerates of tactile end organs of different sizes from a part of the whole section represented in *B*. Note sheaths of connective tissue dividing the nodules into bundles. Van Gieson stain; green filter; × 16⅓.

B, semischematic drawing of *A*. An extension of the tumor is composed of nodules (*1* to *11*), which are surrounded by a sheath more or less rich in connective tissue, resembling a perineural sheath (*P*). Septums of connective tissue like endoneural sheath (*E*) divide the nodules into many bundles. These contain tactile end organs, which individually are encircled by collagenous fibrils of connective tissue from the endoneural-like sheath. The detailed structure is shown in a few nodules only.

the cells were flattened and curved with their cytoplasm showing affinity for trinitrophenol in Van Gieson–stained sections. The centrally placed nuclei of these cells were oblong and somewhat smaller than the nuclei of the surrounding fibroblasts (fig. 3).

Some of the corpuscles were very large, with several layers of capsule cells, which were more densely packed toward the periphery (fig. 2 *B*). Some of the corpuscles resembled lamellated tactile bodies.

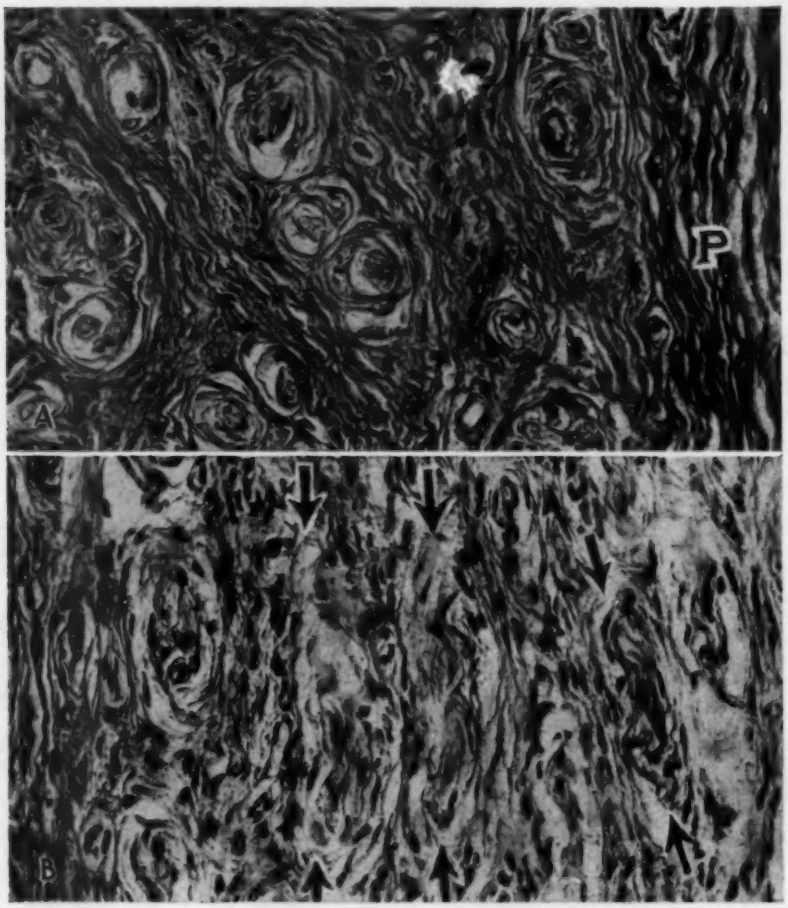

Fig. 2.—*A*, rounded tactile end organs of different sizes surrounded by collagenous fibrils of connective tissue constituting the perineural (*P*) and endoneural sheaths. Mallory-Azan stain; × 312.

B, elongated end organs with the same structural details as in the rounded types. The poles are marked by arrows. Van Gieson stain; green filter; × 312.

The shape and the size were not always easy to distinguish, especially in folded types. In some instances quite minute corpuscles were situated close together in small rows, encapsulated by a common layer of elongated capsule cells. In the longest corpuscles short septums were often seen to project from the capsule

into the central core. Scattered among these relatively big corpuscles small ones were found, the capsules of which consisted of a single layer of cells with thin, fibril-like trinitrophenolophilic cytoplasm. In some of the nodules these minor types of corpuscles were gathered in small groups ("primary bundles") or chiefly composed the nodules of the tumor (fig. 1 *B*, nodules *7*, *8*, *9*, *10* and *11*).

In order to get a more precise idea of the size of the corpuscles, they were measured in a Van Gieson-stained section, illustrated in figure 1 *A* and figure 2 *B*. In this section the contour of the corpuscles was distinct, owing to the affinity of the capsule for trinitrophenol, which gave a precise contrast to the fuchsinophilic connective tissue. The longest and shortest axes of the corpuscles with their capsule cells were measured by means of an ocular micrometer.

The number of corpuscles in the different nodules varied greatly. The nodules labeled *1* to *11* in figure 1 *B* contained the following numbers of corpuscles: *1*—331; *2*—380; *3*—364; *4*—56; *5* and *6*—*6*; *9*—96; *8*—37; *9* and *10*—14; *11*—3, or a total of 1,287 corpuscles.

The longest axes varied between 8.1 and 226.8 microns. The mean value (M) was 43.4 microns, with a standard deviation (σ) of $\pm$ 27.3 microns. As to the shortest axes, the values lay between 5.2 and 113.4 microns, with the mean (M) 26.3 microns and the standard deviation (σ) $\pm$ 17.6 microns.

The central part of the corpuscles consisted of some few cells with finely vacuolated cytoplasm and fibrils of connective tissue, which in Van Gieson-stained sections showed a trinitrophenolophilic and fuchsinophilic character, respectively. The number of these cells varied a little, and the cells were mostly placed in the central part of the corpuscle (figs. 3 and 4). Between the collagenous fibrils appeared clear spaces and clefts, the nature and the development of which were not easy to understand. Sudan-stained sections made clear that the corpuscles were free from lipoids. In silver-impregnated sections the centrally placed cells stood out as individual elements with a distinct nucleus and membrane (fig. 3 *F* and *G;* fig. 4 *a*, *b* and *d*). The cytoplasm did not contain any pigment.

The demonstration of silver-impregnated nerve fibers within the corpuscles and in the connective tissue was of the greatest importance for the classification of the tumor. These nerve fibers penetrated the capsule at one pole of the corpuscle (*x* in fig. 3 *B*). Both the number of nerves and their caliber varied. Many thin parallel fibrils or one thick fiber accompanied on each side by thinner fibrils could be packed so closely together as to resemble a tactile nerve disk. The main nerve fiber was mostly situated in the axial part of the corpuscles (fig. 3 *A*, *x* in *B*, and *I;* fig. 4), but could also run circularly along the periphery (fig. 3 *D* and *E*). Between the thick and thin nerve fibers appeared thin anastomotic fibrils. These thin fibrils constituted a wide-meshed fibrillar network (fig. 4 *e*).

When the main axial nerves from the periphery were examined, characteristic findings were noted in most of the corpuscles. The nerve lay on the axial side of the nucleus of the tactile cell and showed an arborization or a periterminal network (figs. 3 *C* and 4 *b*). This partly covered the nucleus on the side opposite that facing the point where the nerve entered the corpuscle (fig. 3 *A*, *D*, *F* and *H*). The periterminal thin fibrillar network of the nerve lay just outside the nucleus and distinctly within the cytoplasm (fig. 3 *C* and *F* to be compared with the schematic figs. 4 *a* and *b* and 3 *A*). As seen from the same figures, the extension of the periterminal network could vary somewhat; the meshes could be wider or smaller, and in some specimens only a black impregnated mass was observed.

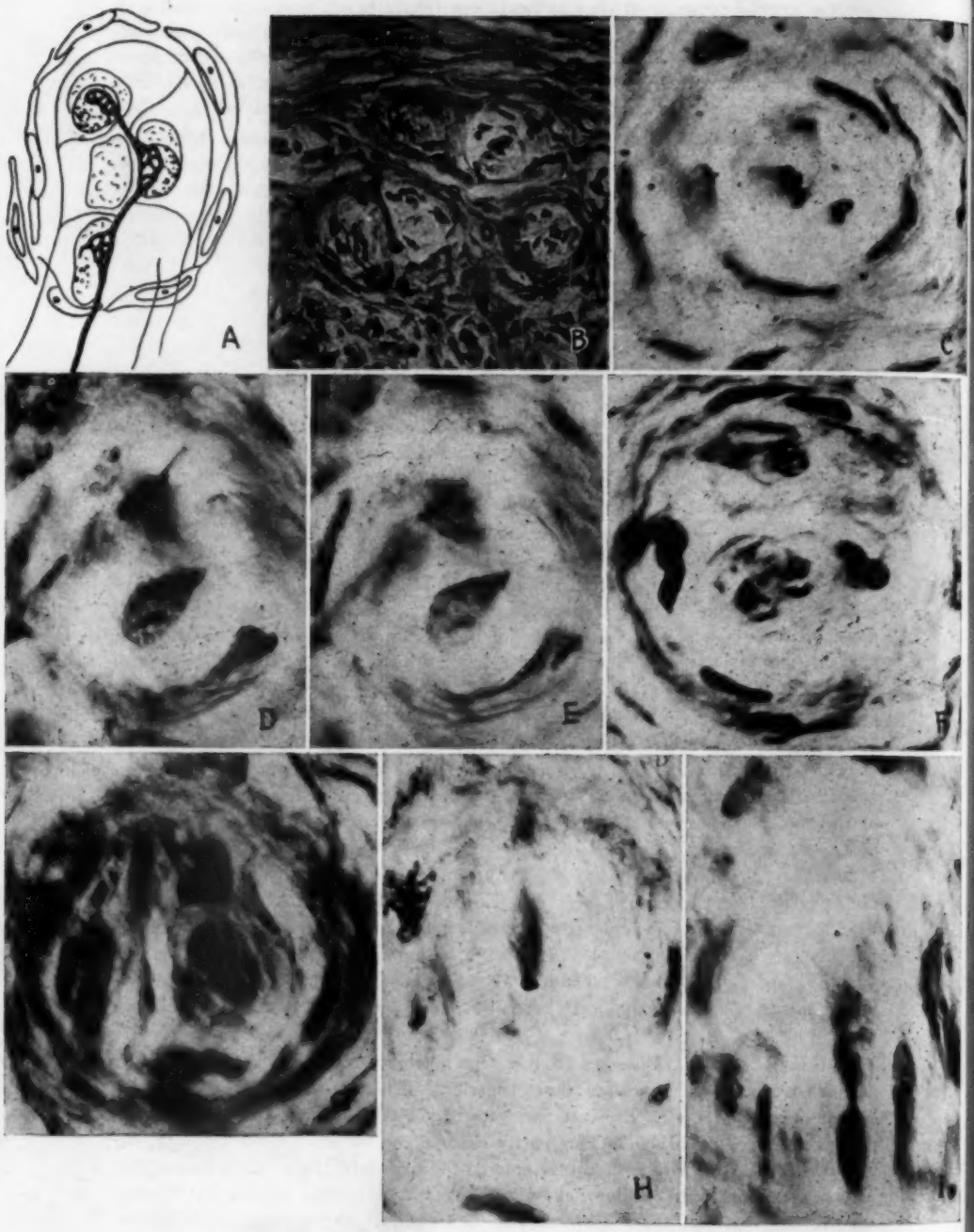

Figure 3

(See legend on opposite page)

The nerve passing the tactile cell membrane showed striking differences in its silver-impregnated appearance. Intracellularly the nerve was somewhat thicker and not quite as smooth as it was outside the tactile cell. This phenomenon was found in the corpuscle illustrated in figure 3 *F* and *G*, but owing to the high magnification used in these photomicrographs, the nerve is not seen in its full extension. In a semischematic drawing the remarkable change of the nerve is illustrated (fig. 4 *a* from the same focus).

Another peculiar finding appeared occasionally in oblong corpuscles in which the axial main nerve trunk passed along the nuclei of several tactile cells (fig. 3 *I* and the corresponding schematic fig. 4 *c*). The nerve then showed a swelling with the endoneural fibrils spread apart. These fibrils covered a part of the nucleus. Along the same nerve were thus seen as many oblong swellings as there were tactile cell nuclei passed.

Other staining methods did not disclose any noteworthy findings, no deposition of lipoid granules, no pigments of melanin or iron and, especially, no distinct myelin sheaths.

Summarizing the findings of the anatomic examination, one may say that the tumor consisted of a mass of fibrous connective tissue which surrounded nodules or conglomerates of tactile end organs. In appear-

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EXPLANATION OF FIGURE 3

A, schematic drawing of the composition of the tactile end organs as observed in the present tumor. Note the flattened cells (showing affinity for trinitrophenol in Van Gieson-stained sections), which encapsulate the corelike central part with nucleated tactile cells. The nerve fiber covers each nucleus with a network situated within the cytoplasm. Thin anastomosing fibrils connect the nerve fibers and fibrils of different calibers. The collagenous fibrils are not taken into consideration.

B, comparatively clear corpuscles with impregnated nerves of varying caliber, distinctly seen in *x* but only faintly in *y*. Silver impregnation after Bodian; yellow filter; × 286.

C, centrally placed, fine-meshed, black-impregnated, periterminal network covering part of an indistinctly seen nucleus; a small triangular part of the cytoplasm of a grayish tone is seen on the right. At the lower right is seen a similar hooklike part of a terminal ending. Compare with figure 4 *b*. Silver impregnation after Bodian; yellow filter; × 1246.5

D, black masses of periterminal network covering part of a nucleus near the lower right corner. The nerves continue as parallel curved bands along the periphery of the corpuscle, also visible in *E*.

E, same field as *D* with moderately changed focus. Centrally placed is a large nucleus of a tactile cell with an indistinct network on the upper right side. Compare with figure 4 *d*. Silver impregnation after Bodian; yellow filter; × 1246.5.

F, dark budlike periterminal network near the centrally placed nuclei of the tactile cells, at the lower left.

G, same field as *F* with changed focus, showing the gathering of the branches from the terminal network into a distinct lightly curved nerve just below a nucleus with a definite nucleolus. (For proper comparison with *F*, *G* should be turned 90 degrees to the left.) The nerve passes outside the nuclear membrane, and within the cytoplasm the contour of its membrane appears more vaguely. Compare with figure 4 *a*. Silver impregnation after Bodian; yellow filter; × 1246.5.

H, terminal ending of the nerve at the top of an indistinctly seen central nucleus. From below thin fibrils bend toward the left side of the nucleus. For proper comparison with *I*, *H* should be turned 180 degrees.

I, continuation of the nerve from the budlike termination in *H* with the fibrils spreading over nuclei of the tactile cells which the nerve is to pass. Compare with figure 4 *c*. Silver impregnation after Bodian; yellow filter; × 1246.5.

ance this highly differentiated tumor resembled in many ways enlarged nerves with different layers of connective tissue or sheaths comparable to the epineurium, perineurium and endoneurium of the peripheral nerves. Each end organ was surrounded by capsule cells

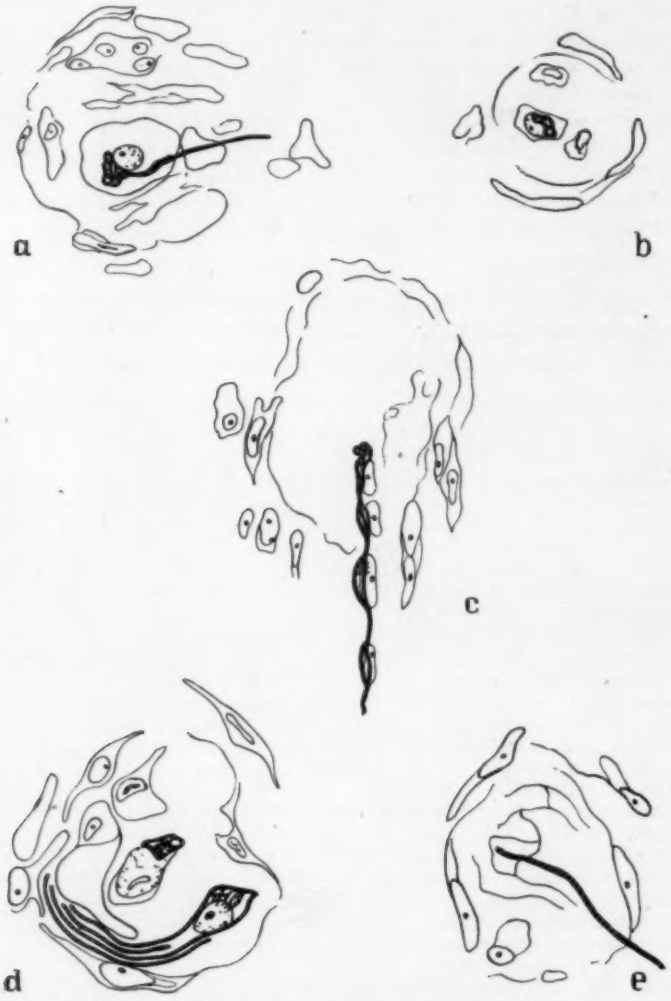

Fig. 4.—Schematic drawings of the corpuscles as they were seen in the fields illustrated in the photomicrographs: *a* from figure 3 *F*, *b* from figure 3 *C*, *c* from figure 3 *H*, *d* from figure 3 *D* and *e* from a photomicrograph not reproduced. See explanation in the text.

which in their tinctorial characteristics might be identified as Schwann cells or derivatives from the ectoderm. The central part of each corpuscle showed a corelike structure with collagenous fibrils taking

the fuchsin of the Van Gieson stain or the blue tone of the Mallory stain. In silver-impregnated sections nerve fibers were seen in the intercorpuscular connective tissue as well as in the corpuscles themselves. The fibers were of different caliber, and as more or less compact parallel threads they followed an irregular course through the axial part of the corpuscle or even circularly along the periphery. The main nerve ran along the axial side of the elongated tactile cell nucleus and showed intracellularly a swelling or a terminal arborization which partially covered the aforementioned nucleus. A wide-meshed network of thin fibrils connected the thin and thick nerve fibers.

COMMENT

Comparing the present case with the previously published cases, no appreciable similarity could be proved. The neoplastic or tumor-like hypertrophy of end organs described by Thoma,[2] Axmann,[3] Brøgli,[5] Scherer [6] and Masson [7] showed another structure than the present case.

One may only point to the peripheral localization of the intracorpuscular nuclei and the onion-like lamellation of the corpuscle, neither of which was characteristically present in the case described here. Scherer,[6] in his case, described a greenish yellow color of some collagenous fibrils found in the core, in contradiction to the red tone of the same parts in my Van Gieson–stained sections. In the two observations which are most similar to the present case, viz., Brøgli's case [5] and Scherer's case,[6] silver-impregnating methods were not used.

The present tumor contained multiple tactile end organs or corpuscles. When these were examined for details, the number of nerves, their course and their caliber showed great variations. It was therefore not possible to demonstrate one corpuscle typical for the whole tumor. A rigorous classification of the different types of corpuscles which constituted the tumor was not carried out, owing to the fact that a thorough comparison with the many descriptions already published on normal tactile corpuscles was impossible (Dogiel,[8] Smirnow,[9] Timofeyeff,[10] Michailow [11] and others). These studies have revealed a great number of normal anatomic facts. However, among the older investigations one may find that a new name has been given to a corpuscle when only a slight variation was observed. Most histologists nowadays are more inclined to distinguish only between a few groups of end organs with typical structure, since the smaller divergencies

8. Dogiel, A. S.: Arch. f. mikr. Anat. **41**:62, 1893; **59**:1, 1902; **64**:173, 1904.

9. Smirnow, A.: Internat. Monatschr. f. Anat. u. Physiol. **10**:241, 1893.

10. Timofeyeff, D. A.: Anat. Anz. **11**:44, 1895; Ergebn. d. Anat. u. Entwcklngsgesch. **7**:627, 1897.

11. Michailow, S.: Anat. Anz. **1**:81, 1907; Anat. Hefte **41**:495, 1910.

should be regarded as the expression of individual variations (van de Velde;[12] Støhr;[13] Boeke [14a]).

The structure of the tactile end organs in the present case confirmed many observations as to normal anatomic features, especially that as to the intracellular localization of the periterminal network (compare van de Velde [12] and Boeke [14a]). The changes noted in the physicochemical property of the nerve as it passes the tactile cell membrane and as demonstrated in silver-impregnated sections cannot so far be explained.

As in the normal tactile corpuscles, the nerve fibers of different caliber were associated in a common network. The meshes contained the tactile cells and the collagenous fibrils. Apart from the remarks of Scherer,[6] no special reference to the tinctorial properties of this central part of the corpuscle was found in the other papers. Most students arrived at the conclusion that the central corpuscular structure was of a collagenous nature. Boeke [14b] mentioned a network of nerve fibers built on "a connective tissue bed." Further discussion of the development of the fuchsinophilic fibrils within the tactile bodies would take one far away from the scope of the present investigation. Many possibilities could be envisaged—for instance, the result of reactive changes, the product of malformation and the peculiar property of the lemnoblastic cells. Uncertainty also arises from the fact that one cannot determine the true nature of the tissue elements or their genetic association from present histologic staining methods (Scherer [15]).

The present tumor, which contained well developed tactile corpuscles, did not give any subjective sensation to the patient. In other cases of hypertrophy of similar organs, however, as in the glomic tumor of Masson,[7a] the patient usually does not complain of pains, or the pains are present only for a short period. Masson expressed the belief that a glomic tumor may elicit pain during its growth by compression of a pacinian corpuscle in the neighborhood. The tumor itself does not seem to have any receptive power. In the present case the deep situation of the tumor and the surrounding masses of connective tissue may have prevented the corpuscles from receiving their proper stimuli. From the anatomic study it is impossible to state which impulses the corpuscles in casu may respond to (Støhr [13]; Boeke [14a]; Barcroft [16]), although physiologic experiments have demonstrated convincingly that

12 van de Velde, E.: Internat. Monatschr. f. Anat. u. Physiol. **26**:225, 1909.

13. Støhr, P., in von Möllendorf, W.: Handbuch der mikroskopischen Anatomie der Menschen, Berlin, Julius Springer, 1928, vol. 4, pt. 1, pp. 143-201 and 202-264.

14. Boeke, J., in Penfield,[22] vol. 1, (*a*) p. 241; (*b*) p. 300.

15 Scherer, H. J.: Virchows Arch. f. path. Anat. **291**:321, 1933; footnote 6.

16. Barcroft, cited by Bazett.[18]

touch, pain, cold and heat act on different corpuscles (Bronk [17]; Bazett [18]; Woollard [19]; Lewis [20]).

As for the genesis of the tumor, one may believe that the normal development has been impeded. The nerve fibers, as well as the lemnoblastic cells, destined for the formation of the capsule cells of the tactile organs, have not reached their final localization. A similar theory of a faulty organization of embryonal tissue was emphasized in the development of other neurogenic tumors (Pick and Bielschowsky,[21] Penfield [22] and others). The same point of view was favored by the nodular structure of this tumor and the structure of the connective tissue, which resembled the sheaths of peripheral nerves.[23]

SUMMARY

From the finger of a man 50 years old a tumor was removed, consisting of conglomerates of highly differentiated tactile end organs with silver-impregnable nerve fibers, which were encapsulated in great masses of connective tissue. The connective tissue consisted of collagenous fibrils arranged as in the different sheaths of the peripheral nerves.

The most plausible pathogenetic factor appears to be an inhibitory effect on the development of the nerve endings and their tactile corpuscles.

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17. Bronk, D. W.: A. Research Nerv. & Ment. Dis., Proc. **15**:60, 1935.

18. Bazett, H. C.: A. Research Nerv. & Ment. Dis., Proc. **15**:83, 1935.

19. Woollard, H. H.: Brain **58**:352, 1935.

20. Lewis, T.: Pain, New York, The Macmillan Company, 1942.

21. Pick, L., and Bielschowsky, M.: Ztschr. f. d. ges. Neurol. u. Psychiat. **6**:391, 1911

22. Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 953.

23. N. C. Foot has briefly described, in a neurofibroma removed from the scalp, a nodule closely resembling a pacinian corpuscle which appears to be similar to the first observed hypertrophic type (Pathology in Surgery, Philadelphia, J. B. Lippincott Company, 1945. This book became available in Norway after the present article had been submitted for publication).

PATHOLOGIC ASPECTS OF ATMOSPHERIC BLAST INJURIES IN MAN

MAJOR HILLIARD COHEN *
AND
COLONEL GERSON R. BISKIND †
MEDICAL CORPS, ARMY OF THE UNITED STATES

DURING World War II, in many countries both the military and the civilian population were exposed to the destructive effects of the detonation of high explosives. As a result, blast injury assumed great importance, and its study was the immediate concern of a number of investigators on the home fronts and in the battle zones. Interest in the problem was particularly great in the Armed Forces, since the Navy had to deal with immersion blast and the Army with atmospheric blast. Though the incidence of injury due to blast undoubtedly was high among military personnel, the number of recorded detailed clinico-pathologic observations on soldiers dying from this type of injury was small.

Thus in the files of the Army Institute of Pathology there are available the records and the material of but 11 cases in which the information concerning the circumstances of the blast is adequate and the lesions are unmistakable. Although the series is small, it is of importance, for hitherto most observations on the pathologic aspects of injuries due to atmospheric blast have been based on animal experimentation.

CLINICAL NOTES

CASES 1 to 6.—The 6 patients will be considered as a group, since fatal injuries in all resulted from the same accident. A heavy bomber, returning from a mission, crash-landed in an ammunition dump in which there was a large quantity of high explosive (trinitrotoluene). The plane immediately burst into flames. Soldiers stationed at the dump and at installations nearby ran to the scene of the crash to rescue the crew from the burning plane. Suddenly a terrific explosion occurred, and an unknown number of soldiers were caught in it. Six who survived the immediate effects of the blast were evacuated to an Army hospital, where they arrived less than an hour after the explosion.

At entry most of the patients showed various degrees of shock and restlessness; 1 was stuporous. A bloody, frothy fluid filled the mouth and the nose, respirations were labored, both exposed and unexposed parts were burned, and widespread punctate hemorrhagic lesions showed where particles of debris had been forcibly

From the Army Institute of Pathology, Army Medical Museum, Washington, D. C. and the 362d Medical Laboratory.

* Now at Mount Sinai Hospital, New York.

† Now at Mount Zion Hospital, San Francisco.

driven into the skin. There were no significant surface or penetrating wounds and no fractures of bones. The lungs revealed severe bilateral pulmonary edema; at no time were clinical signs of consolidation evident.

Treatment of the burned and shocked patients included the usual supportive measures: injection of plasma, administration of morphine and application of pressure bandages to the affected parts. Serum albumin was administered to 1 patient. Penicillin in the amount of 40,000 units was given to all patients with burns every two hours. Blood pressure readings were recorded for 4 patients; in 3 the low pressure noted on admission was successfully combated only to fall terminally; in the fourth the shock level of the pressure persisted. In most instances suction had to be employed to clear the mouth and the upper respiratory passages of the bloody, frothy fluid. Dyspnea and pulmonary edema persisted; the restlessness of 2 patients changed to excitability, irrationality and mania. Death was attributed to respiratory failure and shock. The periods of survival are recorded in table 1. A roentgenogram of the chest of the patient who survived seventy-one hours showed "generalized diffuse areas of density throughout both lung fields."

Case 7.—The soldier was in the vicinity of an explosion of stored dynamite. He died ten minutes later. There were no burns, no significant external wounds and no fractures of bones.

Case 8.—The soldier was in a gun emplacement when a 500 pound (227 Kg.) aerial bomb exploded nearby. When he arrived at an evacuation hospital five hours later, he was in profound shock. Despite vigorous antishock therapy and continuous administration of oxygen, the blood pressure continued to fall, and the patient died thirty-six and a half hours after the blast. There were no significant external wounds, no burns and no fractured bones.

Case 9.—The soldier was in a hospital tent when a buzz bomb (V-1) landed and exploded 40 feet (12 meters) away. On admission to the hospital he was unconscious and in shock, his respirations were gasping and irregular, subcutaneous emphysema was apparent, and there was bloody froth in the mouth. With treatment for shock the respirations improved, but subsequently fell to 2 per minute. A roentgenogram of the chest revealed pneumothorax on the left side with mediastinal shift. This condition was successfully relieved by insertion of a flutter valve. Ten hours after the accident the patient regained consciousness, but the respirations and the heart action remained irregular. Fine and coarse rales were diffusely audible in both lungs. A roentgenogram forty-eight hours after the explosion showed changes consistent with blast injuries in both lungs. During the fourth day the patient suddenly became worse; he was disoriented and excitable. All reflexes were hyperactive, but no pathologic reflexes were obtained. The blood pressure was 150 systolic and 75 diastolic. He died on the fifth day, one hundred and twelve hours after the explosion. There were no burns or fractured bones. The only significant external injury was a penetrating wound of the right upper arm, measuring 5 by 3 cm.

Case 10.—The soldier was assisting in the rescue of personnel from a burning plane when bombs which were stored in the plane exploded. The clinical findings were: first and second degree burns of the face and of the right upper and lower extremities, shock, hemoptysis, oliguria and rales in both lungs. There were no fractures or significant external wounds. He died in approximately forty-eight hours.

Case 11.—The soldier was caught in an explosion of dynamite. Shock, coma and generalized dusky cyanosis rapidly developed. The cyanosis responded to

continuous administration of oxygen. Suction had to be employed frequently to clear the pharynx of accumulations of bloody fluid. Death occurred eighteen hours after the accident. There were no burns and no fractures, but there were numerous superficial abrasions and contusions of the skin of the face, the chest and the upper and lower extremities.

PATHOLOGIC OBSERVATIONS

The number of hours which elapsed from the time of death until autopsy varied from two to seventeen hours. Six of the 11 patients had surface burns, the degree and the extent of which are indicated in table 1. In 5 the skin of the trunk and occasionally that of the face, the neck and the extremities was peppered with minute hemorrhagic burns or lacerations. These lesions involved the entire thickness of the skin, and a few extended into the superficial subcutaneous tissue. In the center of each a tiny piece of debris or dirt was embedded. In case 3 a laceration, 1.2 cm. in diameter, and numerous hematomas were present in the scalp of the frontal region; in case 9 a penetrating wound in the right upper arm measured 5 by 3 cm. No significant surface or penetrating wounds were found in the remaining cases, but in the majority there were superficial abrasions or lacerations of the skin over the body (table 1). Inspection and palpation revealed no fractured bones. The muscles of the trunk and the extremities were free of hemorrhage or other signs of injury. The parietal pleura in case 7 showed numerous petechiae; in the remaining cases neither the parietal pleura nor the peritoneum was hemorrhagic or lacerated, and the intercostal vessels were not torn.

The significant lesions in our cases were in the lungs. Since the gross and the microscopic pulmonary changes were fundamentally similar in all the cases of the series they will be described collectively. Lesions of other organs occurred with much less regularity, but in some instances were no less striking than those of the lungs.

Lungs.—(*a*) Gross Findings: The lungs were large and heavy, the increase in size and weight affecting both the right and the left lung roughly to the same extent. The average weight of the right lung in this series was 1,020 Gm.; that of the left lung 875 Gm. Visible externally were numerous, diffuse, often discrete zones of pleural or subpleural hemorrhages, or both, deep purple-red discolorations, which varied considerably in size, the smallest ones ranging from a few millimeters to 2 cm. in diameter, the largest involving the surface of almost an entire lobe. The hemorrhages showed no tendency to follow the costal markings. In 4 of the 11 cases large amounts of blood had collected beneath the pleura at the interlobar reflections near the hilus. Section of the substance of the lungs revealed many, scattered, solid, dark red, hemorrhagic zones, usually clearly defined; these also exhibited wide variations in size. Occasional large confluent hemorrhages were from 9 to 12 cm. in greatest diameter, and in 1 instance almost an entire lobe was converted into a hemorrhagic mass. The distribution, as well as the size of the hemorrhages, was variable. Some were confined to the subpleural zone, with the remainder of the lobe free of hemorrhage. Other subpleural hemorrhages overlay a relatively nonhemorrhagic layer of parenchyma, with hemorrhage repeated in the underlying tissues. Sometimes the deeper portions of the lung were hemorrhagic while the more superficial parts were not. Finally, some hemorrhages involved the entire thickness of a lobe. In this series of cases the hemorrhages showed no predilection for either lung, a given lobe of either lung or a particular portion of the lobe. Thus the hemorrhages were bilateral, the upper lobes were affected as frequently as the

lower lobes, and the anterior portions were involved as frequently as the posterior portions. In an individual case the hemorrhages were more intense in one lung or in a given portion of a lobe, but in the over-all picture they were bilateral and multilobar and spared no part of the lungs.

The pulmonary parenchyma surrounding the hemorrhages was diffusely pink-red and markedly edematous. In almost every case the dark red hemorrhagic zones stood out in sharp contrast to the surrounding acutely hyperemic and edematous parenchyma. Large amounts of pink, frothy and frankly bloody fluid dripped freely when the lungs were cut. This bloody and frothy fluid also filled the lumens of the bronchioles, bronchi and trachea and was frequently found in the mouth and the nares. The respiratory passages themselves were free of significant changes.

Gross intrapulmonary emphysema and tearing of the lung parenchyma were observed in only 1 case; laceration of the visceral pleura, in none. Pneumothorax

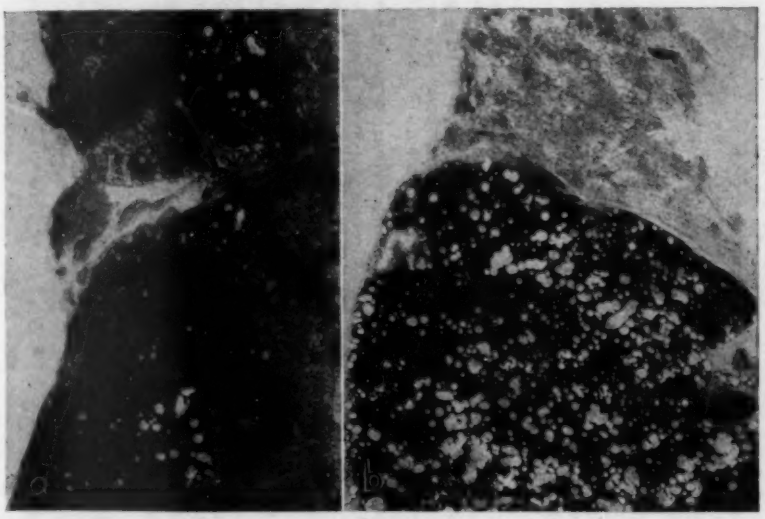

Fig. 1.—(*a*) Two contiguous pulmonary lobules. In both there is intense hemorrhage. The interlobular septum is focally hemorrhagic. × 4. (Army Institute of Pathology negative 90905). (*b*) Intense intrapulmonary hemorrhage affecting one entire lobule and completely sparing a contiguous one. The interlobular septum is free of hemorrhage. × 3.8. (Army Institute of Pathology negative 90906.)

(unilateral) occurred in 1 case. Free liquid blood was found in the pleural cavities in 7 cases, the hemothorax being bilateral in 6 and unilateral in 1. The amount of blood in the pleural cavity was never in excess of 400 cc., usually between 50 and 125 cc.

(*b*) Microscopic Changes: The principal lesions were acute hemorrhages, edema and emphysema. The distribution of the hemorrhages was inconstant. Some extended throughout the whole of two or more contiguous lobules (fig. 1 *a*); others filled entire lobules but spared adjacent ones (fig. 1 *b*), while many involved only parts of single lobules. The hemorrhages varied in intensity as well as in extent. In the profoundly hemorrhagic zones all alveoli, alveolar ducts and respiratory bronchioles and the majority of the larger bronchioles were distended by closely packed erythrocytes. In these areas the alveolar septal

TABLE 1.—*Summary of Clinical and Postmortem Findings in Eleven Cases of Atmospheric Blast Injuries*

Case	Age	Race	Sex	Survival Time	Surface Burns and/or External Wounds	Weight of Lungs, Gm.	Pathologic Findings in Lungs	Pulmonary Fat Embolism	Effects on Other Structures
1	21	W	M	17½ hr.	First and second degree, face, chest, upper and lower extremities, (approximately 40 per cent of body surface); skin of trunk peppered with minute hemorrhagic burns	Rt. 900 Lt. 800	Intrapulmonary hemorrhages and edema, severe, in all lobes, bilat., most pronounced in lower lobes; severe vesicular and minimal interstitial emphysema; bilat. hemothorax, 50-75 cc.	Moderate	Hemorrhages, diffuse, in thymus and perithymic tissues
2	22	N	M	8 hr.	None	Rt. 1,000 Lt. 930	Intrapulmonary hemorrhages and edema, severe, in all lobes, bilat.; mod. vesicular emphysema; bronchopneumonia; bilat. hemothorax, 300 cc. rt., 50 cc. lt.	Minimal	Hemorrhages, focal, small, in epicardium, myocardium, adrenal gland cortex, kidney
3	25	W	M	Less than 1 hr.	Second and third degree, head and face; laceration and hematomas of scalp; skin of neck, trunk and upper extremities peppered with minute hemorrhagic burns; superficial abrasions of lower extremities	Rt. 1,000 Lt. 1,000	Intrapulmonary hemorrhages, severe in 4 lobes; edema, severe, in all lobes, bilat.; mod. vesicular emphysema; bilat. hemothorax, 50-100 cc.	None observed	Petechiae in epicardium; hemorrhage, diffuse, mod., in leptomeninges
4	29	W	M	4 hr.	Second degree, face, ant. part of neck, right side of chest and axilla, upper and lower extremities, above and below elbows and knees; post. part of trunk peppered with minute hemorrhagic burns	Rt. 1,070 Lt. 900	Intrapulmonary hemorrhages (chiefly subpleural to av. depth of 2 cm.) and edema, severe, in all lobes, bilat.; mod. vesicular emphysema; bilat. hemothorax, 125 cc.	None observed	Hemorrhages in mesentery (7 x 9 cm.), leptomeninges (diffuse, mod.), cortex of rt. temporal lobe (focal); petechiae in epicardium
5	31	W	M	18 hr.	First and second degree, face, neck, chest, left forearm, hands, lower extremities	Rt. 1,250 Lt. 900	Intrapulmonary hemorrhages (chiefly post.) and edema, severe, in all lobes, bilat.; mod. vesicular emphysema; bronchopneumonia	Moderate	Acute perforation of sigmoid; gen. peritonitis; hemorrhages, focal, in testis, spleen; occasional microscopic perivascular hemorrhages in brain

6	27	W	M	71 hr.	First and second degree, face, hands and lower extremities; small superficial hemorrhagic laceration of upper ant. part of chest	Rt. 920 Lt. 910	Intrapulmonary hemorrhages (chiefly subpleural to av. depth of 2-3 cm.) and edema, mod. in all lobes, bilat.; minimal vesicular emphysema; antemortem thrombi in mod. numbers of pulmonary vessels; hyaline membrane coating of alveolar walls	Moderate	Large hemorrhage in wall of stomach; occasional microscopic hemorrhages in leptomeninges and brain; bilat. perforation of tympanic membranes
7	20	W	M	10 min.	No burns; peppering of minute lacerations in skin of major portion of ant. surface of body; penetrating wounds of both eyes; left lower incisors fractured at gingival margin	Rt. 1,450 Lt. 1,350	Intrapulmonary hemorrhages and edema, severe, in all lobes, bilat.; severe vesicular and interstitial emphysema; small subpleural air blebs visible grossly; much disruption of pulmonary tissues near hil.; bilat. hemothorax, 25-50 cc.	None observed	Mediastinal emphysema; small hemorrhages in thymus, parietal pleurae, epicardium, pelvis of kidney
8	22	W	M	36½ hr.	No burns; small contused abrasion of right forearm	Estimated 3 times normal	Intrapulmonary hemorrhages and edema, severe, in all lobes, bilat.; bronchopneumonia	Minimal	Hemorrhage in diaphragm in vicinity of esophageal hiatus
9	22	W	M	112 hr.	No burns; small contusions, lacerations and abrasions, superficial, face, right upper extremity, left ankle; penetrating wound of right upper arm, 5 x 3 cm.; skin of left ant. part of chest studded with minute spots	Rt. 1,000 Lt. 525	Intrapulmonary hemorrhages, severe in all lobes of rt. lung; minimal, in left lung; atelectasis of left lung; left pneumothorax; bilat. hemothorax, 300-400 cc.; antemortem thrombi in mod. numbers of pulmonary vessels	Minimal	Subcutaneous and mediastinal emphysema; petechiae in omentum and in perirenal and periadrenal tissues; large tear and massive hemorrhage in cerebellum; punctate hemorrhages in cerebrum; diffuse leptomeningeal hemorrhage in cerebrum and cerebellum
10	31	W	M	48 hr.	First and second degree, face, right hand, thigh, knee; superficial abrasions of chest, left arm and leg; hemorrhage in conjunctiva of left eye	Rt. 650 Lt. 750 (Weights estimated)	Intrapulmonary hemorrhages and edema, moderately severe, bilat.; hyaline membrane coating of alveolar walls	Minimal	Petechiae in endocardium, epicardium; microscopic hemorrhages in myocardium, spleen; focal necroses in spleen; venous thromboses in spleen, heart
11	20	W	M	18 hr.	No burns; hemorrhages in conjunctivas of both eyes; superficial abrasions and contusions of face, chest, upper and lower extremities	Rt. 960 Lt. 680	Intrapulmonary hemorrhages and edema, severe, in all lobes, bilat.; mod. vesicular emphysema; bronchopneumonia; rt. hemothorax, 150 cc.	Minimal	Internal hemorrhage in left eye; hemorrhages in colon; microscopic hemorrhages in myocardium, brain

markings usually were clearly defined but occasionally had disappeared, leaving a large confluent hemorrhage. In the areas of less intense hemorrhage the alveoli, the alveolar ducts, the respiratory bronchioles and some of the larger bronchioles contained varying amounts of edema fluid in which erythrocytes when present were not closely packed. In the routinely prepared hematoxylin-eosin sections it appeared that many alveolar septums were thickened from hemorrhagic infiltration. By the use of the reticulum stain (Wilder's method) it was found that the majority of these septums were of average thickness and the reticular structure was intact. Actually the hemorrhage had occurred in the alveoli, and the erythrocytes had been displaced peripherally against the septal walls by the large volume of intra-alveolar air. Nevertheless there was unmistakable bleeding into some of the septums. In the foci of intense hemorrhage the peribronchiolar and perivascular supporting tissues, the intralobular septums

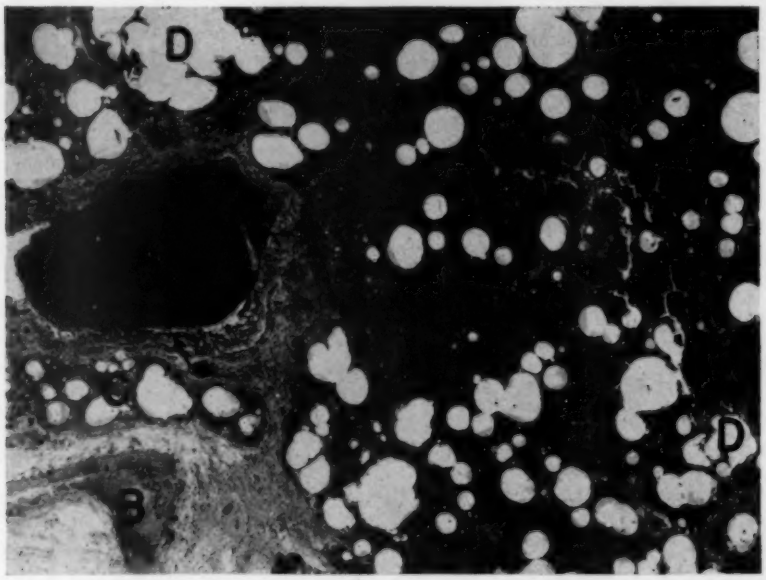

Fig. 2.—Intense intrapulmonary hemorrhage, severe diffuse vesicular emphysema and focal interstitial emphysema. *A* indicates a bronchiole filled with an erythrocyte cast; *B*, a congested pulmonary vessel; *C*, interstitial emphysema in a bronchovascular septum; *D*, torn and fragmented alveolar septums. The arrow indicates a site of focal ulceration of the bronchiolar epithelium with intense hemorrhagic infiltration of the exposed lamina propria. × 25.4. (Army Institute of Pathology negative 90899.)

and occasionally the interlobular septums were heavily infiltrated with erythrocytes and edema fluid. These tissues were not affected in patches of less intense hemorrhage. In the nonhemorrhagic areas of the lung, intra-alveolar and intrabronchiolar edema was common.

Severe acute emphysema, noted frequently, was practically always of the vesicular variety, was diffuse and occurred in both the densely and the less intensely hemorrhagic portions of the lung. The alveoli, the alveolar ducts and the respiratory bronchioles were the air passages most constantly involved, the larger bronchioles occasionally. The alveolar septums were at times seen to be

lacerated and fragmented in areas of severe emphysema (fig. 2). Although numerous sections of lung were studied, interstitial emphysema was found in only 2 cases. One focus, located in a bronchovascular septum, is clearly demonstrated in figure 2.

Changes were often observed in the walls of the bronchioles. The earliest change appeared to be a loosening or lifting-off of the epithelium from the underlying bronchiolar wall, with displacement or shedding of the epithelium into the lumen. The epithelial detachment was partial or complete and sometimes had progressed to fragmentation and disappearance of the epithelium. Usually the lamina propria remained attached to the wall, but occasionally it too was partially or completely denuded to expose the internal surface of the bronchiolar musculature. At the site of epithelial denudation intense hemorrhagic infiltration of the lamina propria might take place (fig. 2). In the space formed when the epithelium separated from the lamina propria, edema fluid often collected, and occasionally the space contained extravasated erythrocytes in moderate numbers

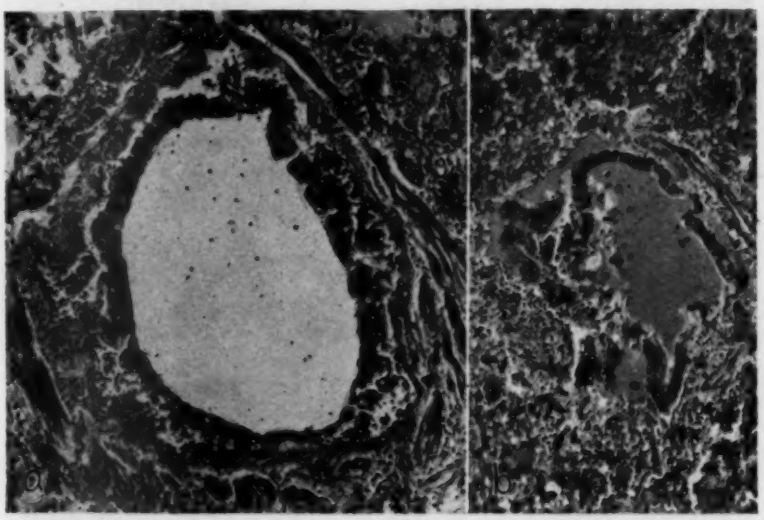

Fig. 3.—(*a*) Complete detachment of bronchiolar epithelium. Extravasated erythrocytes in moderate numbers have accumulated in the space formed where the epithelium separated from the lamina propria. × 109. (Army Institute of Pathology negative 92361.) (*b*) Bronchiole showing detachment of the epithelium, edema fluid in the lumen and edema fluid and groups of erythrocytes in the space formed by the separation of the epithelium and the lamina propria. × 109. (Army Institute of Pathology negative 92362.)

(fig. 3*a*). In practically every instance in which a subepithelial collection of edema fluid was noted, there was an associated accumulation in the lumen of the bronchiole (fig. 3*b*). At times the lifted-off epithelium was interrupted, establishing continuity between luminal and subepithelial edema. Frequently polymorphonuclear leukocytes infiltrated the wall of the bronchiole in minimal to moderate degrees, being usually concentrated in the lamina propria and often completely sparing the muscle (fig. 4*a*). Unless there were secondary purulent bronchiolitis and bronchopneumonia (both were rare) the leukocytes almost always were limited to the wall of the bronchiole and were not in the surrounding parenchyma. Occasionally, however, leukocytes in moderate numbers did appear in the peri-

bronchiolar tissue when the lamina propria of the bronchiole was infiltrated (fig. 4*a*). Usually the mural leukocytic infiltration was associated with partial or complete ulceration or loss of epithelium; occasionally it was seen when the epithelium was intact but loosened (fig. 4*b*). In all instances the epithelium appeared to be well preserved and viable. The bronchi did not show significant histologic alterations.

Engorgement of the pulmonary vessels was constant in the intensely hemorrhagic zones but variable in the remainder of the lung. Tears of the walls of

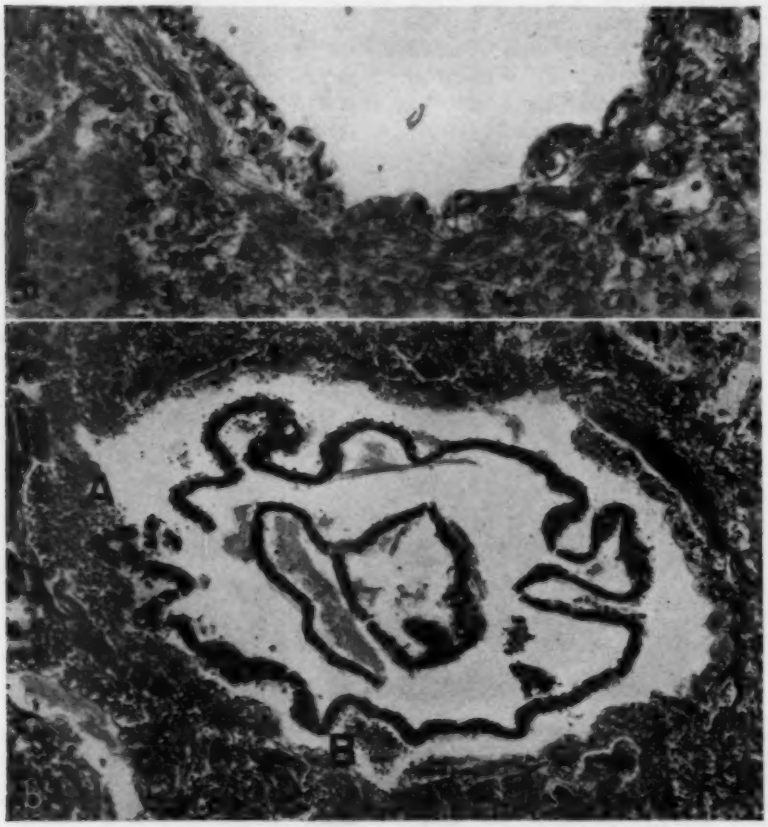

Fig. 4.—(*a*) Bronchiole showing complete epithelial ulceration and moderate leukocytic infiltration of the swollen lamina propria. The muscularis is free of inflammatory reaction. In the peribronchiolar tissue moderate numbers of leukocytes are present. × 248.8. (Army Institute of Pathology negative 92552.) (*b*) Complete detachment of the bronchiolar epithelium. Leukocytes in large numbers have diffusely infiltrated the wall, chiefly the lamina propria. The leukocytic infiltration is heaviest at *A*. At *B* a pool of erythrocytes has accumulated in the subepithelial space. The lumen of the bronchiole is free of exudate. × 88.8. (Army Institute of Pathology negative 92363.)

pulmonary veins or arteries were never found. Antemortem thrombi were seldom noted. In the intensely hemorrhagic areas the septal capillaries usually were empty and collapsed (probably due to compression by the intra-alveolar blood),

in contrast to the congestion of the capillaries in sections of the lung which showed edema, moderate hemorrhage or no hemorrhage. As a rule, the lymphatics were dilated and congested.

The visceral pleura was frequently hemorrhagic. The pleural hemorrhage was sometimes directly continuous with a subjacent parenchymal hemorrhage (fig. 5*a*). Sometimes a relatively nonhemorrhagic zone of parenchyma lay between the hemorrhagic pleura and a deep-seated parenchymal hemorrhage (fig. 5*b*), or the lung substance was intensely hemorrhagic and the overlying pleura entirely free of hemorrhage (fig. 5*c*).

Minimal to moderate inflammatory cellular infiltration (principally polymorphonuclear leukocytes and large mononuclear cells) occurred in the hemorrhagic and the nonhemorrhagic portions of the lung in almost every case. A leukocytic response sufficiently heavy to be considered bronchopneumonia was present in 4 cases, with survival times from eight to thirty-six and a half hours.

In all the cases sections of the lungs were stained for fat. Intravascular fat was present in moderate amount in 3 cases and in minimal amount in 5 cases; it was absent in 3.

In case 6 (survival time seventy-one hours) pulmonary hemorrhages, edema and emphysema, though present, were much less pronounced than in the other 10 cases. More conspicuous in this case were (1) a deeply eosinophilic homogeneous hyaline or finely granular material in many of the alveoli and (2) antemortem thrombi in moderate numbers of the pulmonary vessels. This structureless eosinophilic material appeared as sheets filling most of the lumens of the affected alveoli or as thin films or membranes coating the alveolar walls. This phenomenon of the coating of the alveolar walls with a hyaline-like material was also observed in case 10 (survival time forty-eight hours). The material gave a negative staining reaction for fibrin. It probably represented an intra-alveolar transudate which had been displaced peripherally against the alveolar walls. Moderate numbers of large mononuclear cells and a few polymorphonuclear leukocytes were intermixed with some of the sheets of material in the alveoli.

Other Organs and Structures.—Changes attributed to blast effect were found in many organs and structures other than the lungs. A summary of the extrapulmonary lesions follows.

(*a*) Heart: There were subepicardial petechiae in 5 cases, subendocardial petechiae in 1 and microscopic hemorrhages in the myocardium in 3. In the center of one of the myocardial hemorrhages was a small artery occluded by an antemortem thrombus. Microscopic venous thromboses were found in the myocardium in 1 case.

(*b*) Spleen: In case 5 there were two parenchymal hemorrhages, the larger measuring 2 cm. in greatest dimension. The organ was not lacerated, and no thrombi were found. In case 10 microscopic zones of hemorrhages and necroses, as well as thromboses of the veins, especially the trabecular veins, were observed.

(*c*) Kidneys: In the left kidney in 1 case was a small cortical hemorrhage, 1 cm. in diameter. In another case there was a microscopic hemorrhage in the pelvis.

(*d*) Adrenal Glands: Hyperemia of the cortex, especially in the zona reticularis, was usual. No frank hemorrhages were seen, but in 1 case microscopic hemorrhages were noted in the cortex.

(*e*) Testes: In 1 case there was a small surface hemorrhage measuring 0.5 to 1 cm. in one of the testes. It involved the tunica albuginea and the subjacent parenchyma (fig. 6*a*).

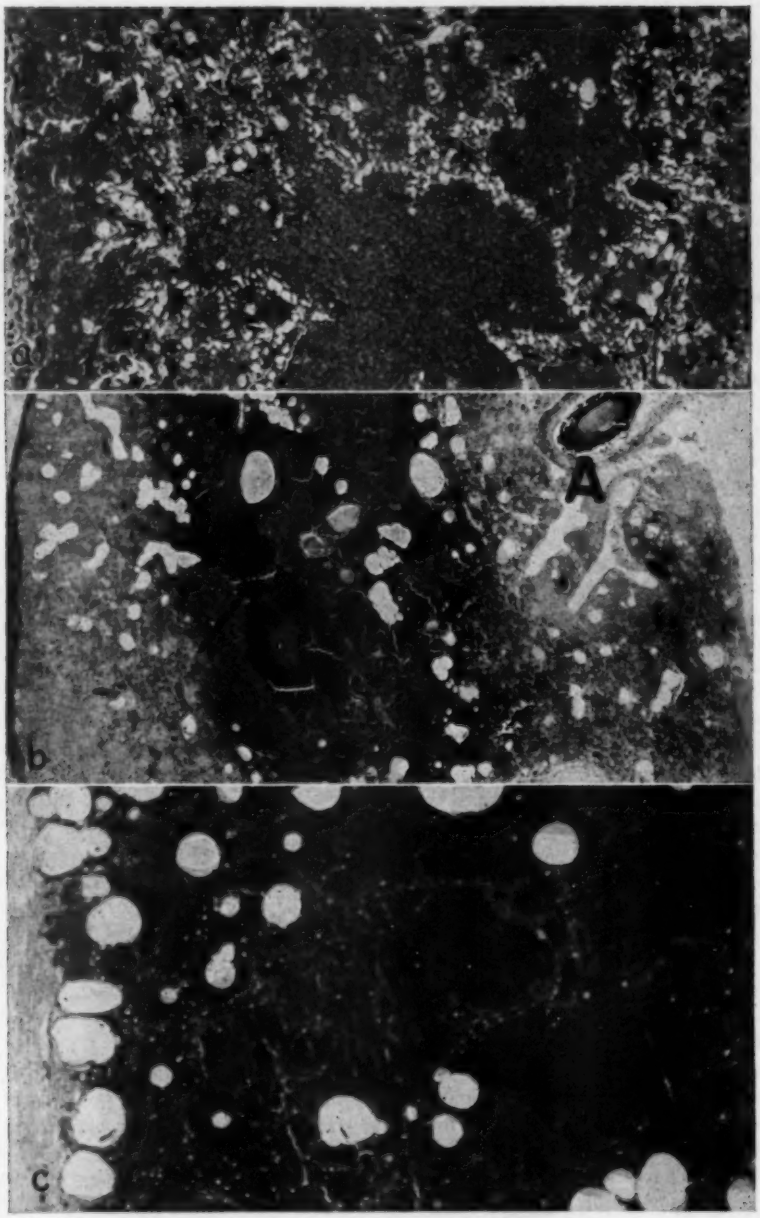

Fig. 5.—(*a*) Intense intrapulmonary hemorrhage involving the pleura and the subjacent parenchyma. × 100. (Army Institute of Pathology negative 90908.) (*b*) Intense intrapulmonary hemorrhage involving the pleura and a deeply seated parenchymal focus. The intervening lung tissue is relatively free of hemorrhage. The thrombus in the large pulmonary vessel at *A* occurred post mortem. × 6. (Army Institute of Pathology negative 90907.) (*c*) Intense intrapulmonary hemorrhage involving the lung parenchyma but sparing the pleura. Small air vesicles are lined up beneath the pleura. × 35. (Army Institute of Pathology negative 90900.)

In all three photomicrographs the pleura is on the left.

(*f*) Mesentery and Omentum: A massive hemorrhage measuring 7 by 9 cm. and several smaller hemorrhages were found in the mesentery in 1 case in which there were no hemorrhages or perforations in the stomach or the intestines. In another, small hemorrhages were seen in the omentum.

(*g*) Gastrointestinal Tract: In 1 case a very extensive hemorrhage of the major portion of the body and cardia of the stomach involved all the layers of the wall, but was especially pronounced in the submucosa and the mucosa. Associated with it were submucosal edema and thrombosis of many of the sub-

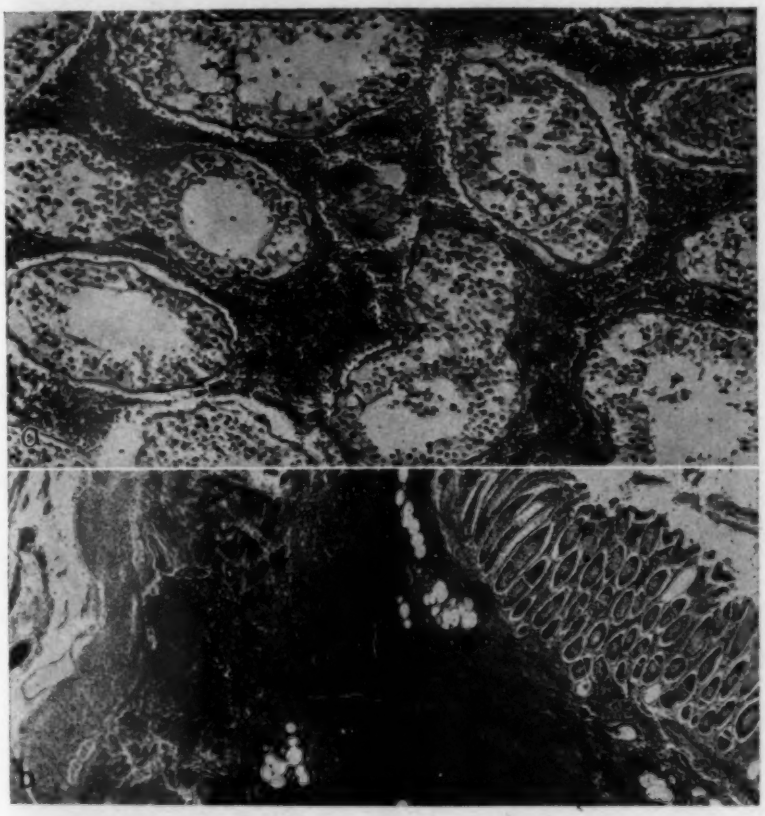

Fig. 6.—(*a*) Testis showing intense hemorrhage in the interstitial tissue. × 116. (Army Institute of Pathology negative 90896.) (*b*) Sigmoid showing intense hemorrhage in the submucosa extending into the inner muscularis. × 14.5. (Army Institute of Pathology negative 90904.)

mucosal vessels, with polymorphonuclear leukocytes infiltrating the area heavily, especially the submucosa and the mucosa. In another there was an acute 2 cm. perforation of the sigmoid opposite the mesenteric attachment, 25 cm. proximal to the anal orifice. In the vicinity of this "blow-out" were extensive hemorrhages especially in the submucosa (fig. 6 *b*), with polymorphonuclear leukocytes heavily infiltrating the entire thickness of the wall of the sigmoid, as well as diffuse fibrinopurulent peritonitis. In a third case the wall of the colon contained patchy, small hem-

orrhages. They were located in the submucosa, the subserosa and the adjacent mesentery.

(*h*) Brain: Pronounced hyperemia of the leptomeninges and the brain substance was a constant finding. Diffuse leptomeningeal hemorrhages, present in 4 cases, were severe in 1 and moderate in 3 (fig. 7 *a*). Intracerebral hemorrhages were noted in 5 cases. In 1 case there were an extensive hemorrhage and a

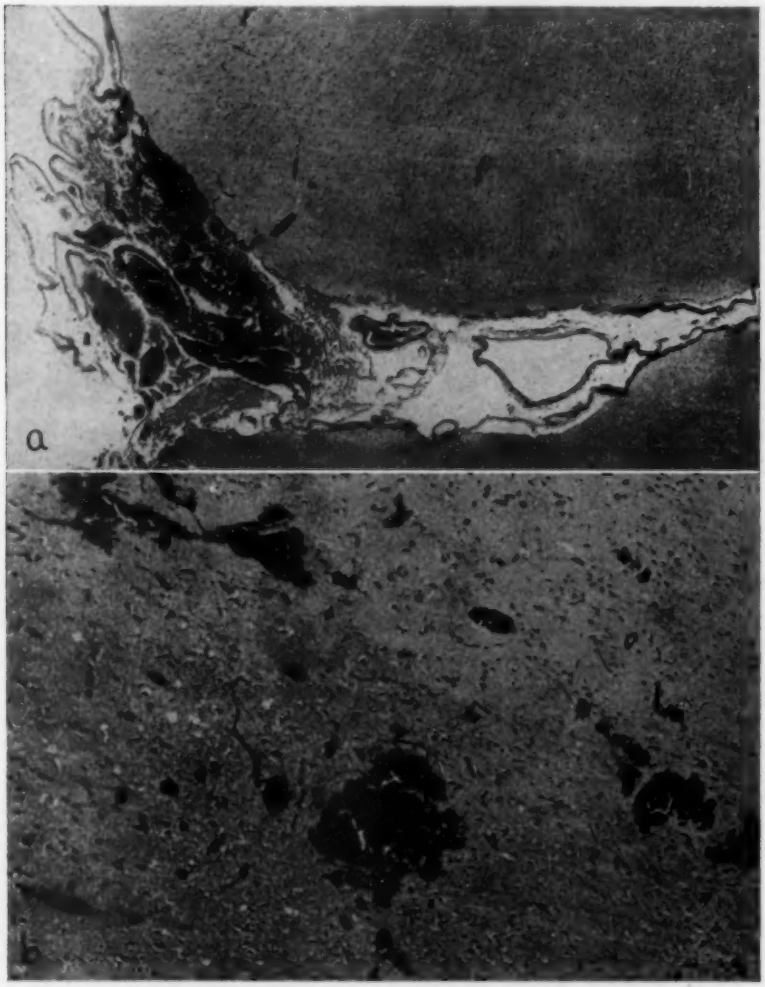

Fig. 7.—(*a*) Focal hemorrhage of the leptomeninges of the cerebrum. × 27. (Army Institute of Pathology negative 90898.) (*b*) Punctate hemorrhages of the cortex of the temporal lobe. × 54. (Army Institute of Pathology negative 90897.)

horizontal laceration in the vermis and both hemispheres of the cerebellum and, in addition, many small punctate hemorrhages in the cerebrum. In another the hemorrhages consisted of multiple, discrete, red, punctiform spots involving 1 to 2 cm. of the cortex of the right temporal lobe (fig. 7 *b*). In the other 3 cases

the intracerebral hemorrhages were seen only microscopically. They were few and were usually located in the perivascular spaces. In 3 cases the intracerebral hemorrhage was associated with bleeding into the leptomeninges.

(*i*) Tympanic Membranes: The tympanic membranes were examined in only 1 case; both membranes were perforated.

(*j*) Eyes: Bulbar conjunctival hemorrhages were noted in 2 cases, and unilateral intraocular hemorrhage in 1 case.

(*k*) Miscellaneous: A large hemorrhage occurred in the thymus and perithymic tissues in 2 cases. In 2 cases there were small hemorrhages in the parietal pericardium. Hemorrhage of the diaphragm near the esophageal hiatus occurred once, mediastinal emphysema twice and subcutaneous emphysema of the chest once.

Gross or microscopic tears were never found in the blood vessels of the organs and tissues in which there were hemorrhages.

(*l*) Liver, Gallbladder, Urinary Bladder, Pancreas, Lymph Nodes, Thyroid Gland and Pituitary Gland: All these lacked lesions which could be attributed to blast injuries.

A summary of the clinical data and postmortem findings is given in table 1.

COMMENT

The term "blast injury" refers specifically to the consequences of the destructive force of the pressure wave set up by the detonation of high explosives. If air is the medium in which the explosion occurs, the term "air blast" or "atmospheric blast" is employed; if water is the medium, "immersion blast" or "underwater blast." The lesions in pure blast injuries are almost exclusively visceral. The bones and the soft tissues of the body wall and of the extremities usually are not involved.

The fundamental experimental studies on the nature, the mode of action and the effects of blast were performed by Hooker [1] and by Zuckerman and associates [2] for air blast and by Williams,[3] Cameron, Short and Wakely,[4] Greaves and associates,[5] Friedell and Ecklund [6] and Friedell and Burke [7] for immersion blast. Zuckerman's comprehensive studies have laid the groundwork for present day knowledge of blast injuries. Physically the blast wave has two components, a positive or

1. Hooker, D. R.: Am. J. Physiol. **67**:219,1924.

2. (*a*) Zuckerman, S.: Lancet **2**:219, 1940 (*b*) Zuckerman, S.; Hadfield, G.; O'Reilly, J. N.; Alston, J. M., and Barsby, B.: Proc. Roy. Soc. Med. **34**:171, 1941. (*c*) Krohn, P. L.; Whitteridge, D., and Zuckerman, S.: Lancet **1**:252, 1942.

3. Williams, E. R. P.: Brit. J. Surg. **30**:38, 1942.

4. Cameron, G. R.; Short, R. H. D., and Wakeley, C. P. G.: Brit. J. Surg. **30**:49, 1942.

5. Greaves, F. C.; Draeger, R. H.; Brines, O. A.; Shaver, J. S., and Corey, E. L.: U, S. Nav. M. Bull. **41**:339, 1943.

6. Friedell, M. T., and Ecklund, A. M.: U. S. Nav. M. Bull. **41**:353, 1943.

7. Friedell, M. T., and Burke, R.: U. S. Nav. M. Bull. **41**:363, 1943.

compression factor and a negative or suction factor.[8] The positive wave attains greater intensity, reaches its peak more abruptly and persists for a shorter time than the negative wave. The duration of each component is only a small fraction of a second.[2a] Because air is less dense and thus more readily compressed than water, water-borne pressure waves reach their maximal intensity later and subside more slowly than air-borne pressure waves. Hence the effects of a given charge of detonated high explosive will be felt over a much greater distance in water than in air. In water to all intents and purposes there is no suction component.[8] Therein lie the essential differences between underwater and atmospheric blast waves. As would be expected, the mode of action and the effects on the body of the two forms of blast are basically similar. Underwater explosions, however, produce intra-abdominal lesions relatively more often than explosions in air, but the characteristic and almost constant lesion in both forms of blast occurs in the lungs.

Critical experiments have demonstrated rather conclusively that the pulmonary lesions of air blast are due to the direct impact on the body wall of the pressure component of the blast wave, not to a sudden rushing of air under pressure down the respiratory tree and into the lungs. The genesis of the gastrointestinal lesions is similar; the intestinal injuries cannot be attributed to a sudden forcing of air or fluid (in the case of immersion blast) into either end of the gastrointestinal tract. The evidence does not support the belief that in air blast the pulmonary lesions result from a lowering of the intrapulmonary pressure by the suction component of the blast wave, acting through the respiratory passages.[2a] The impact of the positive pressure wave on the thoracic wall is primarily responsible for the pulmonary damage, but it is conceivable that the suction wave which follows might add to the insult by pulling out the wall of the chest, thus stretching the already injured lung tissue.[2b]

Perhaps the most characteristic feature of blast injuries is the vulnerability of the air-containing organs and the relative immunity of the solid viscera to the damaging effects of the blast wave. This difference in visceral response to blast is best explained by certain well established physical principles. When a transmitted high pressure wave passes from a medium of greater density (fluid) to one of lesser density (air) a shredding or disruptive effect occurs at the interface of the media.[9] We may consider the soft tissues and the solid parenchymatous organs as representing a fluid medium, and the lungs and the intestine (if gas

8. Sutherland, G. A.: Lancet **2**:641, 1940. Hooker.[1] Zuckerman.[2a]

9. Clark, S. L.: Quart. Bull. Northwestern Univ. M. School **18**:81, 1944. Williams.[3] Greaves and others.[5]

is present in the lumen) a gaseous medium. The blast wave as it passes through the skin, the subcutaneous tissues, the muscles, the liver, the spleen, the kidneys and other structures will produce relatively little damage. But when the pressure wave breaks out of the liquid medium into the gaseous medium (lungs, intestine), the bursting or shredding effect is great enough to produce serious disruption of tissue, resulting in hemorrhage and at times perforation. Ordinarily the stomach and the intestines are resistant, but if gas is present in their lumens the wave will shred as it breaks through.[5] If the gas can be displaced without compression, a hemorrhagic lesion of the wall will be the only result.[5] Perforation will occur when the gas bubble is trapped, becomes compressed under the pressure of the wave and snaps back in reexpansion when the wave passes.[5] If the wall is sufficiently weakened by the shredding injury, the reexpanding bubble will produce a "blow-out" perforation.[5]

A blast wave passing through the body behaves according to a fairly definite pattern, and in every instance it produces constant lesions in man as well as in various experimental animals. The constant and most significant lesion is in the lungs, mainly in the form of extensive bilateral traumatic hemorrhages. Generally the severity of the pulmonary hemorrhages varies directly with the size of the exploding charge and inversely with the distance of the body from the explosion. Hooker [1] regularly found bilateral intrapulmonary hemorrhages in frogs, rabbits, cats and dogs exposed to gun blast. Zuckerman [2a] observed similar lesions after subjecting mice, rats, guinea pigs, rabbits, cats, monkeys and pigeons to detonated charges of high explosive or of hydrogen and oxygen contained in balloons. In man, pulmonary hemorrhages were always found in the cases of blast reported by Falla,[10] Hadfield and co-workers,[11] Hadfield and Christie,[12] O'Reilly and Gloyne [13] and Wilson and Tunbridge.[13a] In our series bilateral hemorrhages of the lungs occurred in all the cases. Zuckerman and co-workers[2c] found that the hemorrhages of the lungs were immediate in onset, as they were observed within one minute after exposure to the blast. Hadfield,[2b] on the contrary, expressed the belief that the maximal amount of intrapulmonary bleeding did not occur immediately, but that the hemorrhages continued, reaching their maximum as much as fifty-one hours later. His opinion was based on the observation that the hemorrhages were smaller when death occurred instantaneously than when there was a period of survival. The

10. Falla, S. T.: Brit. M. J. **2**:255, 1940.

11. Hadfield, G.; Ross, J. M.; Swain, R. H. A.; Drury-White, J. M., and Jordan, A.: Lancet **2**:478, 1940.

12. Hadfield, G., and Christie, R. V.: Brit. M. J. **1**:77, 1941.

13. O'Reilly, J. N., and Gloyne, S. R.: Lancet **2**:423, 1941.

13a. Wilson, J. V., and Tunbridge, R. E.: Lancet **1**:257, 1943.

findings in our cases indicate that the maximal pulmonary damage occurs very early, for the survival time in cases 3 and 7 was less than one hour and yet the hemorrhages were as marked as in any of the other cases, and the hemorrhages in case 6 were the least severe though the survival time was seventy-one hours. That the hemorrhages may not be altogether due to tears or ruptures of alveolar walls seems probable, for, in many areas of hemorrhage histologically intact septums were noted. Both Hadfield [2b] and Cameron, Short and Wakely [4] shared this view. They expressed the belief that the ruptured capillaries were far too few to account for such extensive hemorrhage. They attributed most of the bleeding to diapedesis of red cells. Zuckerman [2b] adhered to the opinion that the bleeding was due primarily to rupture or tearing of the alveolar walls. We failed to find the intense generalized dilation and congestion of septal capillaries reported by Hadfield [2b]; on the contrary, we often observed compressed and empty capillaries in the intensely hemorrhagic patches.

Acute pulmonary emphysema was seen frequently and was almost always of the vesicular variety. Presumably it was due principally to the dilation of alveoli, alveolar ducts and respiratory bronchioles when air became trapped or displaced by a combination of the action of the blast wave and the outpouring of blood. It resulted also from the coalescence of adjacent air spaces when the intervening septums were torn. In only 2 cases did we observe air in the interstitial tissue of the lung. The emphysema was apparent grossly in 1 of our cases. From the results of a series of experiments in which animals were exposed to explosion of underwater depth charges, Cameron, Short and Wakeley [4] were able to correlate the degree of pulmonary damage with the type of emphysema. They found vesicular emphysema in the majority of their animals (regardless of distance from the charge), and interstitial emphysema only in those close to the explosion. In general the animals in the latter group showed the more serious pulmonary damage. The infrequency of interstitial emphysema in our cases suggests that the injury of the lungs must be of the most severe grade before air is driven into the interstitial tissues.

Lesions of the tracheobronchial walls (intramural hemorrhages and occasional epithelial desquamation) are mentioned in the literature on blast injuries.[14] Neither gross nor microscopic lesions were observed in the walls of the trachea and the bronchi in our cases, but the bronchioles shared in the injury of the remainder of the lung, and intramural lesions were repeatedly observed in them. Many bronchioles showed nothing more than loss of epithelium, with or without loss of lamina propria, and minimal to moderate leukocytic infiltration of

14. Zuckerman and others.[2b] Cameron and others.[4] Falla.[10] O'Reilly and Gloyne.[13]

the remaining lamina propria and occasionally of the muscle. The absence of leukocytes in the bronchiolar lumen and of significant inflammatory reaction in the surrounding pulmonary parenchyma suggested that the intramural leukocytic reaction was in response to an intrinsic injury of the bronchioles.

The separation of the epithelium that was often observed in the bronchiolar wall (fig. 3 and 4) is not to be confused with that commonly seen in postmortem material, a phenomenon which pathologists generally regard as an artefact. Such postmortem change differs from the type of separation we have described, since in the former there is no associated hemorrhage, subepithelial accumulation of edema fluid or leukocytic infiltration of the wall. The situation of the bronchiolar epithelium increases its susceptibility to blast injury, because it lies precisely at the fluid-air interface, where the disruptive effect of the pressure wave would strike. There is little room for doubt that blast can cause great damage to the bronchioles.

Examinations have been made for fat embolism in blast injuries by many investigators on material from both experimental animals and man. The results have been repeatedly negative [15] except in the case of an air raid casualty reported by Robb-Smith [16] in which fat embolism was severe and was considered a major cause of death. In all 11 cases of our series sections of the lung were stained (sudan III) for fat. Fat embolism was present in 8; the amount of fat was moderate in 3 and minimal in 5. In the 3 cases in which pulmonary fat embolism was moderate, there were superficial burns. Since fat embolism is known to occur following burns,[17] it is impossible to decide whether in our cases the burns or the blast injuries were responsible for the dissemination of fat. Regardless of the causative agent, we may be reasonably certain that the amount of fat was not great enough in any of our cases to have significantly affected the clinical course or to have been materially responsible for the lesions observed in the lungs. Reports in the literature and our experience justify the conclusion that fat embolism is not an important consideration in the majority of cases of blast injury.

Pneumonia complicating blast injury of the lungs of experimental animals and man has been reported.[18] The pneumonia may develop within a matter of hours after the blast, and the infection may alter the clinical course. In most of our cases there was minimal to moder-

15. (*a*) Wilson, J. V., and Tunbridge, R. E.: Lancet **1**:257, 1943. (*b*) McKibben, P. S.: Am. J. Physiol. **48**:331, 1919. (*c*) Zuckerman and others.[2b] (*d*) Cameron and others.[4] (*e*) O'Reilly and Gloyne.[13]

16. Robb-Smith, A. H. T.: Lancet **1**:135, 1941.

17. Groskloss, H. H.: Yale J. Biol. & Med. **8**:175, 1935.

18. Zuckerman and others.[2b] O'Reilly and Gloyne.[13]

ate exudation of leukocytes and large mononuclear cells in the hemorrhagic as well as in the nonhemorrhagic portions of the lung. However, in only 4 of the cases was the inflammatory response sufficiently heavy to warrant the diagnosis of bronchopneumonia. Notwithstanding the presence of pneumonia, we believe that death was due primarily to the extensive pulmonary damage incident to the blast injury. It is interesting that in 2 of the 4 cases pneumonia developed despite early and continued administration of large doses of penicillin. Conditions under which the autopsies were performed were such that samples from the lungs could not be obtained for bacteriologic study.

Since in 6 of our cases superficial burns were fairly extensive and since burns are known to produce changes in the lungs, the question whether the burns were causally related to the pulmonary lesions must be considered. In burns the principal pulmonary findings are hyperemia, edema and petechiae.[19] Massive pulmonary hemorrhages and severe emphysema are not described, nor have we ever encountered them at autopsy. Furthermore, in the 5 cases without burns the pulmonary lesions were the same as in those with burns, and the lesions were just as pronounced when only a small area of the body was burned as when as much as 40 per cent was involved. We believe, therefore, that the burns were of little or no significance in the causation of the pulmonary lesions.

We may dismiss inhalation of irritant or toxic gases as a possible etiologic factor in the pulmonary lesions in this series. The explosions occurred out of doors in the open air, and the periods of exposure were brief. Furthermore, the hemorrhagic and necrotizing inflammation of the trachea and bronchi seen following inhalation of irritant fumes[20] was uniformly absent.

Carbon monoxide intoxication also may be eliminated because the exposure was in the open air and brief, and the typical cherry red coloration of the blood, the viscera and the muscles was absent. Carboxyhemoglobin saturation of the blood was not determined.

In addition to its effects on the lungs, blast may injure other organs and tissues. In the literature there is reference to involvement of most of the solid parenchymatous organs of the abdomen,[21] the urinary bladder,[2b] the pregnant uterus,[2b] the gastrointestinal tract,[22] the mesentery,[15a] the omentum,[3] the retroperitoneal tissues,[23]

19. Pack, G. T.: Arch. Path. **1**:767, 1926. Erb, I. H.; Morgan, E. M., and Farmer, A. W.: Ann. Surg. **117**:234, 1943.

20. Mallory, T. B., and Brickley, W. J.: Ann. Surg. **117**:865, 1943.

21. Zuckerman and others.[2b] Cameron and others.[4] O'Reilly and Gloyne.[13]

22. (*a*) Ecklund, A. M.: U. S. Nav. M. Bull. **41**:19, 1943. (*b*) Zuckerman and others.[2b] (*c*) Williams.[3] (*d*) Cameron and others.[4] (*e*) Greaves and others.[5] (*f*) Friedell and Ecklund.[6] (*g*) O'Reilly and Gloyne.[13]

23. Williams.[3] O'Reilly and Gloyne.[13]

the anterior and posterior mediastinal tissues,[24] the thymus,[2b] the heart,[25] the aorta (rupture of it),[15a] the soft tissues of the chest and the abdomen,[26] the soft tissues of the neck,[24] the periorbital soft tissues,[2b] the eyes,[3] the tympanic membranes[27] and the central nervous system.[28] There also have been reported hemoperitoneum,[29] hemothorax[30] and hemopericardium.[31] The extrapulmonary lesions almost always were focal hemorrhages in the organs or tissues affected; lacerations were noted but were rare; occasionally perforations occurred in the intestine; in the majority of cases the tympanic membranes were perforated. The hemorrhagic lesions were usually small, but occasionally in the soft tissues of the thoracic and abdominal walls, the retroperitoneal tissues and the anterior and posterior mediastinal tissues the hemorrhages were of huge dimensions. In our series the locations of the hemorrhages are summarized in table 1. It is plain that they were widely distributed. Particular reference should be made to the testicular hemorrhage seen in case 5. No such observation, as far as we have been able to ascertain, has been reported previously in cases of air or immersion blast. The extensive necrosis and venous thrombosis in the spleen in case 10 may possibly be attributed to the burns rather than to the blast. Characteristically in blast injuries there are no significant external wounds and the bones are not fractured unless forcible contact occurs between the victim and some object or hard surface.

We wish to emphasize that in blast injuries (1) the extrapulmonary lesions are inconstant and are usually inconsequential in the ultimate outcome, (2) the pulmonary hemorrhages are constant and account for the characteristic clinical and pathologic features of blast injuries and (3) in the average case the extent and the severity of the pulmonary hemorrhages are the deciding factors in the survival or the death of the patient.

The lesions of the lungs provide the basis for the principal clinical manifestations of blast. The severe pulmonary hemorrhages and edema and the overflowing of blood and edema fluid into the respira-

24. Zuckerman and others.[2b] O'Reilly and Gloyne.[13]

25. Stewart, O. W.; Russel, C. K., and Cone, W. V.: Lancet **1**:172, 1941. Cameron and others.[4] Wilson and Tunbridge.[15a]

26. Zuckerman and others.[2b] O'Reilly and Gloyne.[13] Wilson and Tunbridge.[15a] Ecklund.[22a]

27. Hooker.[1] Zuckerman and others.[2b] Williams.[3] O'Reilly and Gloyne.[13]

28. (*a*) Mott, F. W.: J. Roy. Army M. Corps **29**:662, 1917. (*b*) Zuckerman and others.[2b] (*c*) O'Reilly and Gloyne.[13] (*d*) Stewart and others.[25]

29. Cameron and others.[4] Wilson and Tunbridge.[15a] Ecklund.[22a]

30. Cameron and others.[4] Greaves and others.[5] O'Reilly and Gloyne.[13] Wilson and Tunbridge.[15a] Ecklund.[22a]

31. Zuckerman and others.[2b] Wilson and Tunbridge.[15a]

tory passages are the causes of the respiratory distress. The respiratory rate is usually increased; this appears to be due at first to massive stimulation of the deflation endings in the lung (the compression effect on lungs as the blast wave strikes the chest).[2c] Subsequently, after intense hemorrhage and deformation of lung tissue have occurred, the increase in rate apparently results from the increased sensitivity of the intrapulmonary stretch endings.[2c] The hyperpnea cannot be attributed to chemical changes affecting the respiratory center or to the direct effect of the impact of the blast wave on the medulla.[2c] The early experiments of Hooker[1] indicated that shock, which so regularly occurs in blast, is not related primarily either to

TABLE 2.—*Summary of Symptoms Referable to the Central Nervous System and Pathologic Findings in the Brain in Nine of Eleven Cases of Atmospheric Blast Injuries*

Case	Symptoms and Signs	Findings in Brain
1	Pronounced restlessness	Hyperemia of leptomeninges and brain; no hemorrhages
2	Patient excitable, irrational, maniacal	No lesions
3	Patient dead on arrival at hospital	Diffuse moderate leptomeningeal hemorrhage; hyperemia but no hemorrhages of brain
4	No symptoms or signs mentioned in clinical abstract	Diffuse moderate leptomeningeal hemorrhage; focal, punctate, grossly visible hemorrhages in cortex of right temporal lobe
5	No symptoms or signs mentioned in clinical abstract	Hyperemia of leptomeninges and brain; occasional microscopic perivascular hemorrhages in brain
6	Stupor followed by extreme restlessness and irrationality	Hyperemia of leptomeninges and brain; focal microscopic leptomeningeal and intracerebral hemorrhages
8	No symptoms or signs mentioned in clinical abstract	Hyperemia of leptomeninges and brain
9	Patient unconscious, disoriented, excitable; hyperactive reflexes; bradypnea	Large horizontal tear and massive hemorrhage in cerebellum; punctate hemorrhages in cerebrum; diffuse severe leptomeningeal hemorrhage
11	No symptoms or signs mentioned in clinical abstract	Hyperemia of leptomeninges and brain; occasional microscopic perivascular hemorrhage in brain

the peak blast pressure or to the presence of the intrapulmonary hemorrhages. He stressed, as the causative factor, the duration of the positive pressure component of the blast wave. The more recent studies of Krohn and co-workers[2c] suggest that the contrary is true: namely, that the extent and the duration of the fall in arterial blood pressure are related to the peak blast pressure experienced and to the changes in the pulmonary capillary bed incident to the hemorrhages in the lungs. The extremely slow respiratory rate noted in case 9 in all likelihood was due to the severe damage of the brain. Blast effect on the lungs may be readily detected roentgenologically, since the intrapulmonary hemorrhages cast characteristic shadows.

Symptoms referable to the central nervous system were commonly observed in our series. In table 2 these symptoms and the findings

in the brain are summarized for the 9 cases in which the brains were examined. Special cytologic studies of the nerve cells were not done. In our series it appears that no consistent correlation can be made between symptoms and pathologic findings. Under combat conditions, when casualties are being received in large numbers, detailed clinical observations are not possible. This may apply to case 4, in which despite diffuse leptomeningeal hemorrhages and focal punctate intracerebral hemorrhages, no symptoms referable to the central nervous system were noted. In other cases active symptoms of involvement of the central nervous system are recorded in the absence of brain or meningeal hemorrhages (case 2). In the series of cases of blast injury reported by O'Reilly and Gloyne [13] restlessness, extreme in some instances, was an almost constant symptom; "some subarachnoid hemorrhage" was a postmortem finding in 2. In a case reported by Mott [28a] mania was a prominent symptom. The brain showed scattered subpial and intracerebral hemorrhages, diffuse venous congestion and early chromatolytic changes in the nerve cells. Mott expressed the belief that the vascular lesions were responsible for the acute excitability manifested by the patient. Krohn and co-workers [2c] observed that animals exposed to blast exhibited normal cortical activity for ten to twenty seconds after the explosion and then a subsequent depression (but not a cessation) of activity. In animals struck by a blow on the head the reaction was different; here cortical activity was immediately abolished and reappeared after about three minutes. Their observations also indicated that concussion had not occurred. Zuckerman and co-workers [2b] repeatedly found that blast pressure sufficient to cause death and extensive pulmonary hemorrhages failed to produce any lesions in the brain. In subsequent experiments, in which much higher pressures were employed (many times the lethal level) some of the animals showed hemorrhage and edema in the spinal cord and subpial and intraventricular hemorrhage in the brain, but in the brain substance hemorrhage was not found. It appears evident, then, that blast may produce hemorrhages and certain functional alterations in the brain. The specific role which these play in the causation of the symptoms and the other factors that may be operating cannot be accurately assessed.

SUMMARY AND CONCLUSIONS

The principal and characteristic lesion in 11 selected cases of atmospheric blast injuries was severe diffuse bilateral traumatic hemorrhage of the lungs. All lobes of both lungs and all portions of a given lobe were involved in the hemorrhagic process. Intense edema and emphysema of the lungs occurred almost as frequently as did hemorrhage. The emphysema was predominantly vesicular in type;

the interstitial variety was noted only twice. The bronchioles, though perhaps not so vulnerable as the remainder of the pulmonary parenchyma, also were susceptible to the damaging effects of the blast wave; the epithelium became loosened or detached from the lamina propria, with erythrocytes, edema fluid and leukocytes being extravasated into the injured bronchiolar wall. Pulmonary fat embolism was moderate in 3 and minimal in 5 cases. We regard this degree of fat embolism as neither of significance in the causation of the pulmonary lesions nor of influence in the clinical course of blast injury.

Although the predominant damage of blast is intrapulmonary, none of the soft tissues or other viscera shows absolute immunity to the destructive effects of the blast wave. In every case extrapulmonary lesions occurred in a variety of organs as small hemorrhages or very occasionally as tiny lacerations in the affected structures. In 4 cases striking extrapulmonary lesions were found: In 1 case there was a "blow-out" perforation of the sigmoid; in a second, a massive hemorrhage in the mesentery; in a third, a large horizontal tear and a massive hemorrhage in the cerebellum; in a fourth, an extensive hemorrhage in the wall of the stomach.

Six patients were burned. Though it is recognized that changes in the lungs frequently occur with burns, we are convinced that the burns were not responsible for the pulmonary lesions in this series of cases. It is possible that they were instrumental in causing the pulmonary fat embolism observed in 3 cases and the necrosis of the spleen in 1 case. Bronchopneumonia occurred in 4 cases. Hemothorax was noted in 7 cases, mediastinal emphysema in 2, pneumothorax in 1 and subcutaneous emphysema in 1.

Our findings in general are in accord with the observations of other investigators who have studied atmospheric blast injuries in animals and man.

STRUCTURE OF THE TESTIS IN INFANCY AND IN CHILDHOOD

With a Discussion of the So-Called Underdeveloped Testis

PETER GRUENWALD, M.D.
NEW YORK

THE MINUTE structure of the immature testis has been the subject of a number of investigations reported in the literature. The majority of these previous communications dealt with the problem of defining the normal condition of the testis as observed in infancy and childhood, in order to provide a basis on which the condition of a particular organ may be evaluated. Several early workers in this field brought an unfortunate trend into the investigation of the immature testis by designating the great majority of the organs at their disposal as abnormal. Much of the following work has been concerned with arguments about this point. These and other reports in the literature will be discussed more fully in a later section of this report.

The presence of large numbers of well preserved, presumably normal testes in the material of this laboratory suggested a new examination of the structure of the immature testis. An effort was made to abstain from preconceived criteria of normalcy and to designate as normal that range of forms which must be assumed to develop at puberty into structurally and functionally normal testes.

MATERIAL AND METHODS

All organs used in the present investigation were obtained at autopsies and fixed in Zenker's fluid. The histologic condition of the tissue, rather than the time elapsed between death and fixation, was taken into consideration in selecting the specimens, since it is known that the speed of postmortem deterioration of tissues varies greatly. Sections were thus selected from well over 100 suitable testes and stained with hematoxylin and eosin. Only 1 organ was examined in each case. In 97 cases various special stains and staining methods were employed, such as phloxine and methylene blue, Mallory's connective tissue stain, phosphotungstic acid–hematoxylin, or Foot's or Gomori's silver impregnation of lattice fibers. No use was made of various histochemical or physical methods for the demonstration of substances related to the specific function of endocrine cells,[1] because it was the aim of the study to describe those structural characteristics

From the Department of Pathology, Infants' Hospital and Children's Hospital, Boston.

1. Dempsey, E. W., and Bassett, D. L.: Endocrinology **33**:384, 1943.

which may be demonstrated by the methods available in the average histologic or pathologic laboratory.

The ages of the persons whose testes were studied for the present report ranged from birth to 12 years, including a number of premature infants. The changes at puberty are therefore not included. The age distribution of the specimens studied with special stains (that is, other than hematoxylin and eosin) was as follows: first day, 8; 1 to 7 days, 15; 7 days to 1 month, 14; 1 to 3 months, 15; 3 to 6 months, 13; 6 to 12 months, 11; 1 to 4 years, 11; 4 to 12 years, 10. Testes which were obviously affected by disease were excluded. Almost all organs selected according to their state of preservation were within the limits of what is here considered to be normal. The history and the cause of death were not evaluated in detail in each case. Only in a few instances the question of a developmental disturbance arose, and in those the history was carefully studied.

OBSERVATIONS

The developmental changes will now be described separately for each histologic constituent of the testis. This facilitates the description and involves no considerable disadvantage since there is no obvious correlation of changes in various tissues of the testis during the period under consideration.

Sex Cords and Seminiferous Tubules.—The presence of large numbers of hollow seminiferous tubules is uncommon before puberty. The greeat majority of the organs contain solid sex cords throughout. Embryologically these are primary sex cords, that is, derived from the first generation of cords forming in both sexes during the early phases of gonadal development. The occurrence of the secondary sex cords of the testis will be discussed in the following section.

Several steps of development precede the formation of lumens in the sex cords of the testis. The first of these, recognizable even before birth, consists in a characteristic radial arrangement of the oblong nuclei of the future Sertoli cells within the cords. These nuclei are more densely arranged in the peripheral parts of the cords. A number of the testes of the first year showed this condition, although the majority exhibited the next stage, in which the nuclei are present only peripherally in the cords, leaving a central portion free (figs. 1, 4 and 7). This central area is filled with pale and irregularly staining material forming granules or meshes. It is impossible to determine whether this mass consists of parts of the cell bodies completely or partly filling the central area, or of debris of parts of cells, or of entire cells disintegrating in the center of the cord, or of coagulated extracellular material. There is, however, no free lumen present in this stage of differentiation. Only a small number of specimens showed patent seminiferous tubules, and even in these organs many of the cords were still in the stage just described. When definite lumens were present cells were often seen in them, with large nuclei and cell bodies of irregular form (fig. 5), and one might suspect that they remained behind when the other cells retracted to the periphery. There is no indication that the frequent occurrence of these cells in seminiferous tubules of children is in any way abnormal. Similar cells may also be seen in the centers of cords of the preceding stage.

These changes in the sex cords do not occur simultaneously in all parts of a testis. Thus two or sometimes all three of the stages may be seen in adjacent cords. Their distribution, as far as age is concerned, is so irregular that it could be evaluated statistically only in a material much larger than that at our disposal. In judging single testes, these changes are therefore of minor importance. The

uniformly solid cords, as described in a foregoing paragraph, occur mainly during the first year. Lumen formation, on the other hand, is seen more commonly in the testes of older children. This is not a rigid rule, and the youngest testis with definite lumens in some of its tubules was that of a 1 day old infant. The great majority of the organs examined showed most of their cords having pale-staining centers, described in the foregoing paragraph as the second stage. However, shrinkage due to inadequate preservation may well produce the semblance of lumens in these cords.

The basal membranes of the sex cords will be described in the section on the connective tissue. The spermatogonia show no significant changes during childhood.

Secondary Sex Cords in Normal Testes.—Embryologic studies have shown that secondary sex cords, which were formerly believed to form only in ovaries, also occur in some normal human testes.[2] These cords were found in groups within the tunica albuginea, or between it and the superficial epithelium with which they connect. They often penetrate the tunica albuginea and join with the typical (primary) cords in the interior of the organ. They occur in embryos of varying ages, and no clear concept could be gained of the frequency with which they occur, since they are often overlooked unless serial sections of the entire testis are prepared. Furthermore, it is not known how long these cords can be distinguished from the primary ones, because all or most of them probably join the primary cords and are eventually covered by a newly formed portion of the tunica albuginea, so that they can no longer be distinguished. Meyer[3] described these cords as observed in the testes of 2 fetuses of 7 months, and explained them as being cut off from the rest of the cords by the developing tunica albuginea. More recently Chin[4] described such cords as seen in 6 subjects, including fetuses, infants and children, and explained them in a similar manner. The present material contains 2 testes, of 1 and 9 days, respectively, with similar groups of secondary sex cords (figs. 1 and 2). The aforementioned recent embryologic results allow definitely the explanation of all of these findings as secondary sex cords. It is important to know them as vestigial structures in normal testes, and homologues of normal constituents of the ovaries, rather than adenomatous growths or signs of intersexual development, unless they occur in much larger amounts.[5] From the mechanical point of view, groups of secondary sex cords may be of interest if they pierce or weaken the tunica albuginea. Considering the soft consistency of the interior of the testis, and the firm texture of the tunica albuginea, one may suspect that any weakening of the latter would predispose the testis to rupture from mechanical causes. Five cases of rupture of a testis reviewed by Counseller and Pratt,[6] and a case in which a child was recently treated for this condition at this hospital, emphasize the importance of weak points in the tunica albuginea. (In rupture of a testis the tissue at the site of rupture is usually destroyed and can no longer be examined.)

It is impossible at this time to estimate the frequency of secondary sex cords in the testes of infants and children. The areas are small, and even if they were

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2. Gruenwald, P.: Am. J. Anat. **70**:359, 1942.

3. Meyer, R.: Ergebn. d. allg. Path. u. path. Anat. **15**:430, 1911.

4. Chin, S.: Gann **31**:694, 1937.

5. For a description of large layers of secondary sex cords in testes of intersexes see: Gruenwald, P.: Ztschr. f. Anat. u. Entwcklngsgesch. **103**:278, 1934. Walther, R.: Beitr. z. path. Anat. u. z. allg. Path. **95**:297, 1935.

6. Counseller, V. S., and Pratt, J. H.: J. Urol. **52**:334, 1944.

present in every testis, the probability of seeing them on single sections cut at random might not be greater than the incidence in the present material.

Rete Testis.—Not much need be said about the rete testis. Its tubules develop from thin, solid cords, and lumen formation begins much earlier than in the sex cords. It is well under way at birth, and in all stages examined a part of the rete shows definite lumens. There is considerable variation in the proportion of

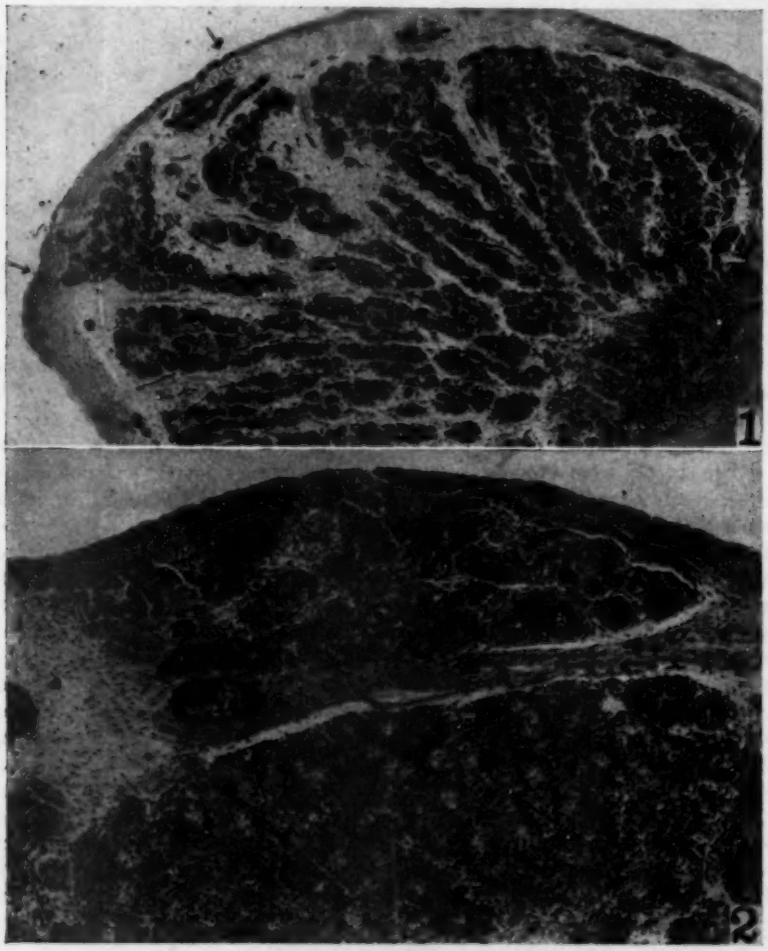


Fig. 1.—Testis of a 1 day old premature infant. A group of secondary sex cords is seen in the tunica albuginea (between arrows). Note a blood vessel of the tunica albuginea between primary and secondary sex cords.

Fig. 2.—Testis of an 8 day old premature infant. A group of secondary sex cords occupies the outer portion of the tunica albuginea.

solid cords and hollow tubules, but a gradual increase in the number of tubules at the expense of cords may be noted during childhood.

Connective Tissue of the Testis.—The connective tissue, as all other constituents of the testis do, shows considerable variation in its development, with the

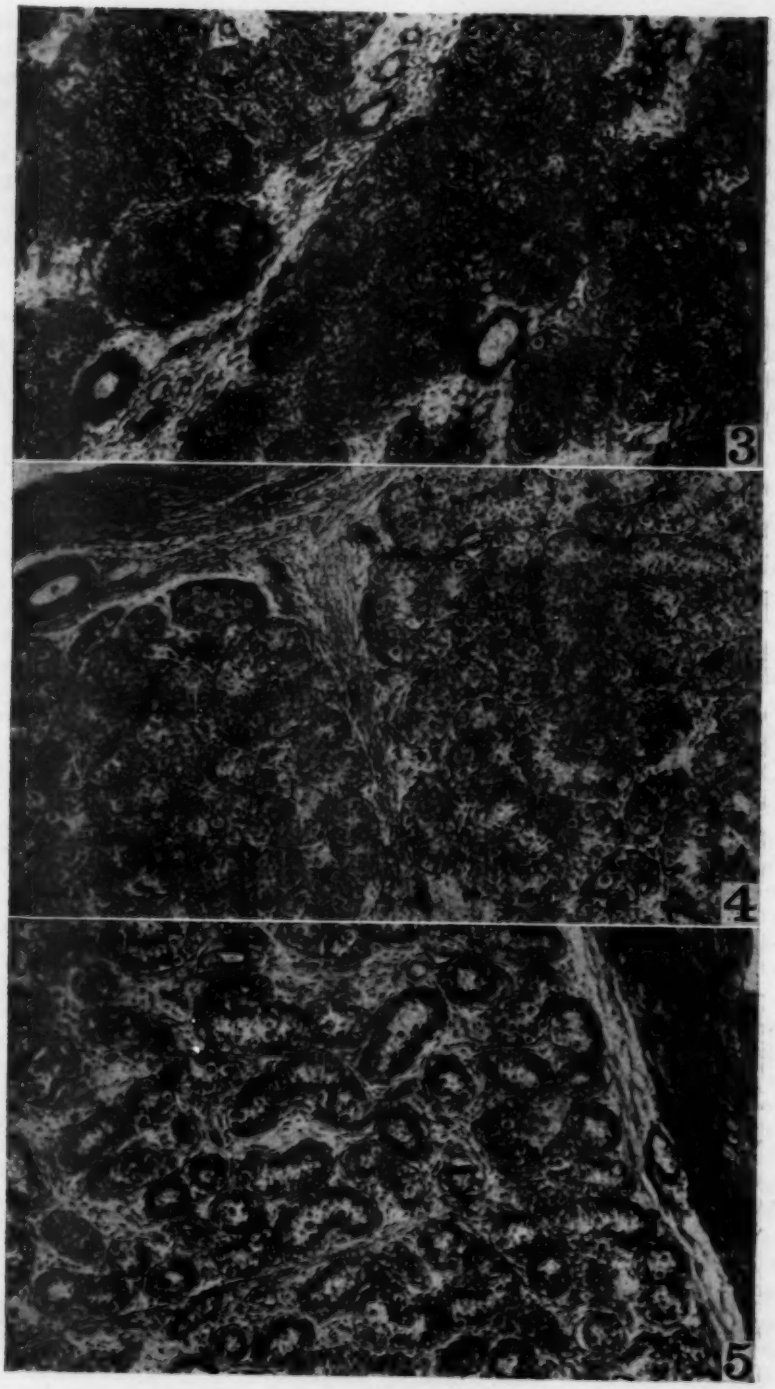
result that a given normal organ may show a condition of this constituent which is more commonly encountered in somewhat earlier or later stages. Yet it appears that the changes in the connective tissue are, when compared with those in the other tissues of the testis, the most regular and reliable of all if one needs to identify the developmental stage of the organ.

Two portions must be distinguished in the connective tissue of the testis. One consists of the tunica albuginea and the septula which extend between the lobules from the hilus to the tunica albuginea. The other portion comprises the intralobular connective tissue which separates the sex cords or tubules from one another in each lobule. The latter portion contains the interstitial cells. The two portions of the connective tissue will now be described separately, and the description of the interstitial cells remains for the following section. The description is based on sections stained by Mallory's aniline blue method or one of its modifications. The fibers staining blue will be considered as collagenous, and all others, showing distinctly only after silver impregnation, as lattice fibers (reticular argyrophil fibers).

In the testis of the newborn the tunica albuginea contains but a narrow peripheral layer of collagenous fibers. The remaining wider zone, as well as the septula, consists of lattice fibers. The only collagenous fibers in the latter areas are seen in the walls of blood vessels. In the course of the first three months of extrauterine life, increasing portions of the loosely textured lattice fiber layers are replaced by, or transformed into, denser masses of collagenous fibers. At the end of this period the entire tunica albuginea contains densely arranged collagenous fibers, which are now in contact with the lobules of the parenchyma. Only in the vicinity of larger blood vessels may larger collections of lattice fibers be found in the inner part of the tunica albuginea. In a few instances the formation of collagenous fibers in the tunica albuginea takes a slightly different course. A new layer of these fibers appears in the inner portion, and is at first separated from the outer one by lattice fibers. The final result is the same in both cases, and none of the older testes showed two separate collagenous layers.

In the septula, too, a gradual increase of collagenous fibers may be seen during this period, and at the age of 2 months the majority of testes contained definite layers of collagenous fibers in the septula. Here, however, considerable variability is encountered, and large numbers of lattice fibers usually remain adjacent to the collagenous fibers for a long subsequent period, While the septula acquire their collagenous fibers, they decrease in thickness.

The intralobular connective tissue apart from the interstitial cells, which will be described later, shows little change in its structure during the first two weeks after birth. Its cells are densely packed, and no collagenous fibers are contained in it (fig. 3). In most testes the sex cords at this stage are separated from one another by connective tissue, although occasional contacts of cords occur in all organs. During the second half of the first month one may notice a tendency toward a looser arrangement of the cells in the intralobular connective tissue. However, the sex cords soon occupy an increasing proportion of the space within the lobules, and at the end of the first month the cords are in contact with one another everywhere (fig. 4). (It should be understood that in the condition designated here as contact of cords, a few fibers and the basal membranes separate the cords.) This condition prevails until, during the fifth month, the cords are again separated from one another by an increase in the intralobular connective tissue. This tissue, however, contains relatively few cells and a delicate network of fibers, some of which take a faint stain with aniline blue when treated by Mallory's method (fig. 5). This condition is fully developed in most testes of



Figures 3, 4, 5.

(See legend on opposite page)

6 to 8 months and persists throughout the period examined, that is, to the age of 12 years or longer.

In many of the specimens the cords are closer to each other in the periphery of the organ than near the hilus. The preceding description applies mainly to the peripheral region.

Hemorrhages have often been described as occurring in the testes at birth. The present material contains a number of organs of young infants in which part of the intralobular connective tissue or of the septula and loose inner portion of the tunica albuginea is the site of hemorrhages, without apparent damage to the sex cords or the general structure of the organ. Most of these hemorrhages are limited to parts of the organ, and many testes of young infants are entirely free of them on section. It is not correct, as one might be led to believe by Stieve's[7] description of the testes of newborn infants, that extensive hemorrhage is the rule.

The basal membranes of the sex cords also undergo a change during infancy. They can be demonstrated only by impregnation of lattice fibers from early fetal periods on until about two months after birth. At that time they begin to stain faintly with aniline blue, and at the age of 6 months the sex cords of all testes have definite collagenous basal membranes.

Interstitial Cells.—The large numbers of interstitial cells present in the testes of the fetus and the newborn infant have aroused much interest and speculation. In view of the numerous discussions of this subject in the literature the present account will be limited to a report of the morphologic changes observed. The cells in question will be referred to as interstitial cells from a purely morphologic point of view, without implying that they are strictly comparable in all respects with the interstitial cells of the mature testis. Of all the commonly used staining methods, phloxine and methylene blue stain proved to show the cytoplasm of the interstitial cells best, and all observations reported in the present section are based on this method. In addition to a large body of acidophilic cytoplasm, a large, pale nucleus is found in almost every interstitial cell. Only in a few instances cells were found which contained in the typical cytoplasm small, dark-staining nuclei.

Interstitial cells are numerous in the testes of many infants of the first week, and they may form large groups within the intralobular connective tissue (fig. 6). It was an exception in the present material to find a testis of the first week with scanty interstitial cells. A slight difference in this respect between full term and premature infants will be discussed in the following section. The

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EXPLANATION OF FIGURES 3, 4 and 5

Fig. 3.—Testis of a 3 day old premature infant (41 cm.). The intralobular connective tissue is so cellular that the sex cords do not stand out distinctly with low magnification. The interlobular connective tissue is loose and contains few cells.

Fig. 4.—Testis of a 2 month old infant. Within the lobules the sex cords occupy a much greater proportion of the space than do those in the preceding figure. The intralobular connective tissue is accordingly scanty. The interlobular connective tissue (septula) is more fibrous than in the early stage.

Fig. 5.—Testis of a child of 3 years and 8 months. The tubules (former cords) are again separated from one another by larger amounts of connective tissue which, in contrast to the early postnatal condition, is loose and poor in cells. It contains delicate fibers which stain blue with Mallory's aniline blue.

7. Stieve, H.: Männliche Genitalorgane, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 7, pt. 2, p. 1.

number of interstitial cells decreases rapidly during the following weeks and is in most cases greatly reduced at the age of 1 month. Few of these cells remain to reach the second quarter of the first year. After this, the presence of interstitial cells cannot be definitely ascertained with the methods used here, and whatever cells then appear at first glance to be interstitial cells usually turn out to be cells of sex cords or small arteries cut tangentially. The common histologic methods do not allow a decision as to whether or not testes between

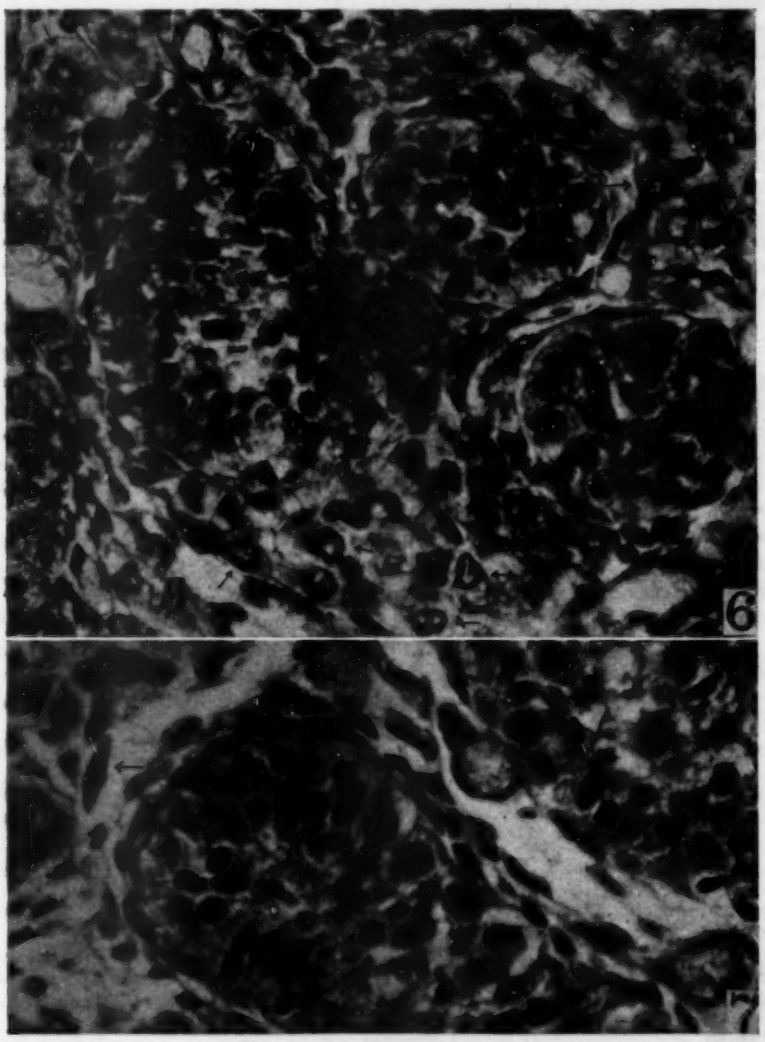

Fig. 6.—Testis of a 3 day old premature infant (41 cm.). The connective tissue between the sex cords contains conspicuous groups of interstitial cells with large, pale-stained bodies of cytoplasm and round or slightly indented nuclei. Some of these cells are marked by arrows.

Fig. 7.—Testis of a 1 month old infant. The connective tissue contains few interstitial cells. The spindle-shaped cell marked by an arrow may be an interstitial cell in the process of transformation into a connective tissue cell.

the age of about one-half year and puberty contain a few interstitial cells. It must remain for special, perhaps histochemical methods to answer this question.

During the period of disappearance the interstitial cells often appear slender, sometimes spindle shaped, with an intensely staining cytoplasm and oblong, deeply staining nuclei (fig. 7). These may be forms intermediate between interstitial cells and fibroblasts—suggesting, as far as morphologic methods allow such conclusions, that interstitial cells disappear by being transformed into fibroblasts. It is doubtful whether entire cells or parts of their cytoplasm disintegrate. Acidophilic granular masses may sometimes be seen in the intralobular connective tissue, but their interpretation as stages in the necrosis of interstitial cells is uncertain. It should be noted that the disappearance of the last interstitial cells that one can safely discern with the usual methods roughly coincides with the appearance of loose intralobular connective tissue during the second quarter of the first year as described on a foregoing page.

Large numbers of interstitial cells are rarely seen in testes of infants older than 1 month. In the present material a testis of a 2½ month old infant with miliary tuberculosis (not in the testis) showed strikingly large numbers of interstitial cells. There were no other signs of retarded or subnormal development in this testis.

Testes of Premature Infants.—Testes of a number of premature infants are included in the present series. It is of considerable interest to see that their development closely parallels that of testes from infants of the same age who were born at term. The number of interstitial cells is often greater in testes of premature infants immediately after birth. This is to be expected since there is normally a decrease in the number of these cells during the last months of embryonic life,[8] and premature children may be born before this diminution has reached its full extent. However, this difference between premature infants and those born at term is not sufficiently large to be evident in any given case. It is apparent only when numerous cases are reviewed. The difference disappears within a few days after birth, apparently because the more numerous interstitial cells of premature infants disappear just as rapidly as do the less numerous cells of others. No other significant difference between these two groups of infants could be detected in the development of the testes. It thus appears that the timing of early postnatal development of the testes is largely determined by extrinsic factors associated with birth and postnatal life, rather than by the actual age of the infant. In the case of the interstitial cells, and perhaps also in regard to other tissues of the testis, it is probable that a change in the hormonal environment plays a leading role.

Subnormal Testes.—It was briefly mentioned before that much of the work on the minute structure of the testis of the infant has been done in order to define "underdeveloped testes" and to determine their frequency which, according to several investigators, is high. Only 3 testes were seen in the present material in which the minute structure differed sufficiently from the standards set in the foregoing pages to be considered as inferior to the normal state. Their ages were 1, 5 and 6 days, respectively (fig. 8). The sex cords were somewhat thinner than usual, and most of them were in the first of the three stages described on foregoing pages. The cells within the cords had a relatively small amount

8. (*a*) Kitahara, Y.: Arch. f. Entwcklngsmechn. d. Organ. **52**:550, 1923. (*b*) Neumann, H. O.: Ztschr. f. Geburtsh. u. Gynäk. **99**:100, 1930. (*c*) Diaca, C.: Virchows Arch. f. path. Anat. **304**:171, 1939. (*d*) Mita, G.: Beitr. z. path. Anat. u. z. allg. Path. **58**:554, 1914.

of cytoplasm, and their nuclei were seen close to one another. However, these changes were not striking; they were significant only in conjunction with findings in the connective tissue. The cords were separated from one another by a large volume of intralobular connective tissue which showed an abnormally loose arrangement of its elements, being similar to the interlobular tissue of this period. This obscured in many areas the demarcation of lobules. The scarcity of interstitial cells in 2 of these organs further contributed to the impression that the sex cords were located in a tissue of the morphologic properties of interlobular connective tissue. One might conjecture that this was due to failure of the subnormal cords to exert the normal formative stimulation on the connective tissue of the lobule. It is of interest to note that 2 of these 3 testes were from infants with multiple malformations. Their number is too small to allow any conclusions. It should further be emphasized that the condition just described

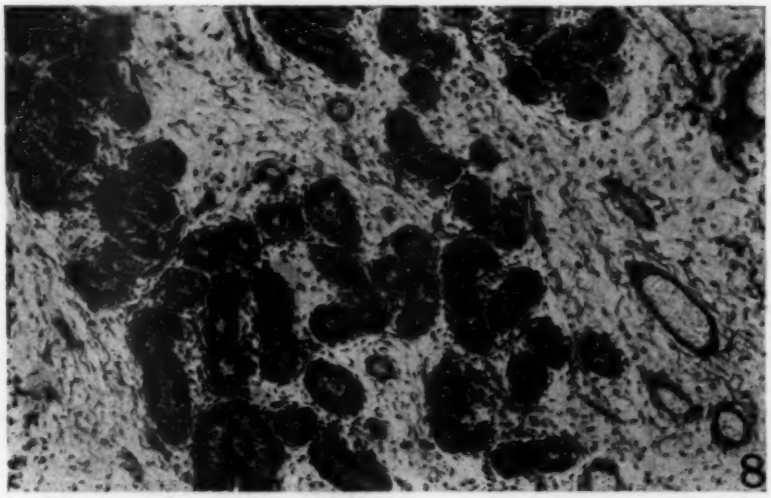

Fig. 8.—Testis of a 5 day old infant. The sex cords are separated from one another by large amounts of abnormally loose intralobular connective tissue which does not differ significantly from the interlobular tissue. Most of the sex cords are in a relatively immature state. This is an example of a subnormal testis. (For comparison with a normal organ, see figure 3.)

bore no similarity to any earlier stage of normal development and was therefore not an expression of retardation.

There were a few additional specimens in which the structure of the cords and the connective tissue was intermediate between what has just been described as abnormal and the normal state. These might be classified differently by various observers, and part of the discrepancies in the literature are probably due to differences in the classification of the borderline cases. Another difficulty in the recognition of subnormal testes arises when the intralobular connective tissue acquires its loose structure at the age of about 6 months. The normal condition after that time is faintly similar to that in subnormal development, and perhaps this accounts for the fact that the diagnosis of subnormal development of the testes was made here only in young infants. On the other hand, it is possible that the normal condition in older children has in the past been mistaken for subnormal development.

COMMENT

An effort has been made to describe the histologic development of the testes of infants and children and to correlate various changes as closely as possible with definite age periods. The principal difficulty encountered in this study is the wide range of variability in the time at which the organs undergo each phase of their postnatal histogenesis. This variability is probably one of the reasons why many investigators, expecting to see a definite condition at a given time, claim to have found an exceedingly high proportion of abnormal testes. In the present interpretation care was taken to draw the limits of normal stages sufficiently wide to accommodate all organs which would probably have developed into normal testes, that is, the great majority.

The most regular, though perhaps not the most essential, changes in the testes of infants concern the connective tissue. Whenever the question of the age of a given normal testis arises, or of what normal stage corresponds to that of a given abnormal organ, a study of the connective tissue may yield the most reliable information, particularly during the first year of life. The changes in the connective tissue described in foregoing pages are most probably not incidental to the development of the other parts of the testis. It may be assumed that here, as elsewhere, the development of the connective tissue is under the stimulative influence of the morphogenesis of the specific cells of the organ and thus reflects their activity to some extent. The structure of the seminiferous tubules, themselves, or their solid primordia cannot be relied on, because any of the stages described here may occur at any age during childhood.

Finding of intestinal cells in the testes of infants are indicative of the age only to a limited extent. These cells are often present in large numbers shortly after birth, and variations in their number seem to depend on individual differences in the speed of their disappearance as well as on the number present at birth. The former factor is not well understood as yet. A change in the hormonal environment at birth is doubtless of great importance, but it does not account for the long persistence of interstitial cells in some otherwise normal testes. Apart from individual differences caused possibly by variations in the hormone concentration to which the fetus was exposed, the number of interstitial cells present at birth depends on the duration of intrauterine life, as already pointed out.

The nature and the fate of the fetal interstitial cells, including those persisting in early infancy, are controversial. That these cells are identical with the interstitial cells of the mature testis cannot be taken for granted; it was emphatically denied by Spangaro.[9] According to

9. Spangaro, S.: Anat. Hefte, 1902, no. 18, p. 593.

Kohn [10] and Neuman,[9b] they develop in the fetus under the influence of hormones of the mother (or the placenta ?); they diminish as the concentration of these hormones decreases during the latter part of pregnancy,[9c] and disappear after birth. Several authors [11] have reported an increase in the number of interstitial cells in the testes of immature rats after the administration of gonadotropic substances prepared from pregnancy urine or serum. This further supports the assumption that the presence of large numbers of these cells in the fetus is a reaction to its hormonal environment. This is then one of the manifestations of mutual influences of mother and embryo, which were brought under the common heading of synkainogenesis by Kohn.[10]

Jaffé [12] held that persistence of numerous interstitial cells with lipoid inclusions in infants and children is part of a peculiar developmental disturbance (*Pädatrophie*). This concept could not be confirmed in the present material. However, the number of testes over 3 months of age with numerous interstitial cells is too small to allow conclusions.

It is commonly believed that close developmental relations exist between interstitial and connective tissue cells in the sense that each kind may transform itself into the other as need may be.[13] Hooker [14] recently described interstitial cells developing from connective tissue cells in the testes of young bulls. The present study revealed, during the period of disappearance of many interstitial cells shortly after birth, cell forms which may well be stages by which they are transformed into connective tissue cells.

Several authors [15] have asserted that the great majority of infants—according to Kryle,[15a] up to 90 per cent—have underdeveloped (*unterentwickelte*) testes. Oberndorfer [16] criticized this view and admitted not more than 20 per cent of underdeveloped testes. It is certainly a misconception of normal structure to decree that only those conditions are normal in which certain supposedly essential parts are

10. Kohn, A.: Arch. f. Entwcklngsmechn. d. Organ. **39**:112, 1914.

11. Moore, C. R., and Price, D.: Am. J. Physiol. **99**:197, 1931. Cole, H. H.: Am. J. Anat. **59**:299, 1936. Price, D.: ibid. **60**:79, 1936. Price, D., and Ortiz, E.: Endocrinology **34**:215, 1944.

12. Jaffé, R.: Frankfurt. Ztschr. f. Path. **26**:250, 1922.

13. Maximow, A. A., and Bloom, W.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1942.

14. Hooker, C. W.: Am. J. Anat. **74**:1, 1944.

15. (*a*) Kyrle, J.: Wien. klin. Wchnschr. **23**:1583, 1910; Beitr. z. path. Anat. u. z. allg. Path. **60**:359, 1915; Wien. klin. Wchnschr. **33**:185, 1920. (*b*) Voss, H.: Centralbl. f. allg. Path. u. path. Anat. **24**:433, 1913.

16. Oberndorfer, S.: Die inneren männlichen Geschlechtsorgane, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 6, pt. 3, p. 427.

"well" developed according to arbitrary standards. The limits of normal structure can be derived only from unbiased study of large numbers of specimens which would later in life presumably develop into functionally and structurally normal organs. We have no right to assume that 90 or even 20 per cent of all men have abnormal testes, and it must be concluded that the quoted authors have not employed proper criteria. Mita [8d] stated that much of what Kyrle regarded as underdevelopment was really edema of the intralobular connective tissue.

Diaca [8c] attacked the same problem experimentally and found that after treatment with hypophysial hormones the solid sex cords of embryos and newborn animals react with a reversible enlargement. He concluded, contrary to the view of Kyrle and others, that testes with thin cords and much intralobular connective tissue are normal and that those with wide cords merely show a reaction to hormonal stimulation.

Considering the aforementioned variability in the normal development of the testis and the normal occurrence of stages with different relative amounts of intralobular connective tissue during the first year, one finds but few cases of subnormal development as I propose to designate it. One cannot accept either one of the quoted concepts according to which normal testes of infants should contain only wide cords and scanty connective tissue, or the opposite. There remains a small number of testes which show narrow and slightly abnormal cords embedded in large amounts of loose intralobular connective tissue at a time when this does not occur in normal organs, and these may be classified as subnormal. However, it is impossible to give concise criteria of this condition, and various investigators would certainly disagree on some cases. It is misleading to call this abnormal condition underdevelopment, because in the minds of many this term means retarded development. Kyrle, himself, having been challenged by Mita, stated that what he called underdevelopment was an inferior condition, different from any normal stage of development. This might better be designated as subnormal.

SUMMARY

The minute structure of the testis in infancy and childhood is described with regard to changes in the sex cords or seminiferous tubules, the connective tissue and the interstitial cells. It is found that the range of variability is wide, so that it is impossible to correlate definite morphologic stages with closely limited age periods. Of all changes described, those in the intralobular connective tissue are the most reliable when one comes to correlate age and structure of immature testes.

Secondary sex cords, forming groups in the tunica albuginea, occur in normal testes of infants as well as in testes of fetuses.

The number of interstitial cells in the testes of newborn infants is variable but usually large. It is perhaps larger in the case of premature infants than in that of infants born at term. However, this difference is not sufficiently great and constant to be regarded as a sign of maturity.

The literature on so-called underdeveloped testes has been critically reviewed and the conclusion reached that if the criteria are properly chosen, the incidence of this abnormality is not nearly as great as has often been suggested.

Long Island College of Medicine, Brooklyn 2, N. Y.

RENAL CHANGES ASSOCIATED WITH A CHLORIDE-DEFICIENT DIET IN THE RAT

ELIZABETH LOWENHAUPT, M.D.
SAN FRANCISCO
AND
DAVID M. GREENBERG, Ph.D.
BERKELEY, CALIF.

THE CHEMICAL changes occurring in tissues and body fluids of the rat fed a diet deficient in chloride have been the subject of previous reports.[1] In brief, these changes consist of a lowering of the concentration of blood chloride, an increase of the concentration of blood bicarbonate and an increase of the urinary excretion of citrate, all indicative of chronic alkalosis. There is a characteristic shift in the water of the body, in which the apparent extracellular phase is increased in most of the tissues. As is the case with most deficiencies, the growth of the rats is stunted. The deficient animals attained only about 50 per cent of the weight of the controls when the chloride content of the diet was reduced to between 2 and 5 mg. per hundred grams of food. The striking renal changes noted previously[1b] in these rats form the subject of the present report.

METHODS

Tissues from the animals used for chemical studies[1b] were fixed in neutral solution of formaldehyde U. S. P. (1:10) and stained with hematoxylin and eosin. In addition, a group of 24 animals was fed the same diet, and the deficient animals, together with the controls, were killed after periods of deficiency varying from six to thirteen weeks. Portions of various organs were fixed in Bouin's fluid, and sections were prepared and stained with hematoxylin and eosin. A portion of kidney of each animal was fixed in cold acetone, and sections were stained to demonstrate alkaline phosphatase by the method described by Gomori[2] and to demonstrate calcium by the von Kossa technic.

RESULTS

Sections of heart, lung and bronchus, liver, spleen, bone and bone marrow, striated muscle, pancreas, hypophysis cerebri and thyroid, parathyroid and adrenal glands showed no abnormalities. (No uniform enlargement of parathyroid glands could be demonstrated, and although some deficient animals showed some thicken-

From the Divisions of Pathology and Biochemistry, University of California.

1. (*a*) Greenberg, D. M., and Cuthbertson, E. M.: J. Biol. Chem. **145**: 179, 1942. (*b*) Cuthbertson, E. M., and Greenberg, D. M.: ibid. **160**:83, 1945.

2. Gomori, G.: Proc. Soc. Exper. Biol. & Med. **42**:23, 1939.

ing and nodularity of the glomerular zone of the adrenal cortex, this was not a uniform finding and could not be demonstrated as a lesion characteristic of deficient animals only.) In male rats late in the deficiency (after eighty days) there was complete atrophy of seminiferous epithelium (fig 1 *B*). Earlier (fig. 1 *A*), numerous giant cells were present in this epithelium, and stages of arrested spermatogenesis could be demonstrated (forty-two days). No changes were found in the ovary.

A uniform lesion was observed in the kidneys. Grossly this was a band of yellowish gray material that involved the intermediate zone,[3] that is, the collecting tubules. In sections stained by the von Kossa method it took on the dark color of calcium (fig 1 *C*). This was the earliest change detectable grossly, although kidneys which appeared normal on gross inspection showed early the microscopic lesions described later. As the deficiency progressed the kidney eventually

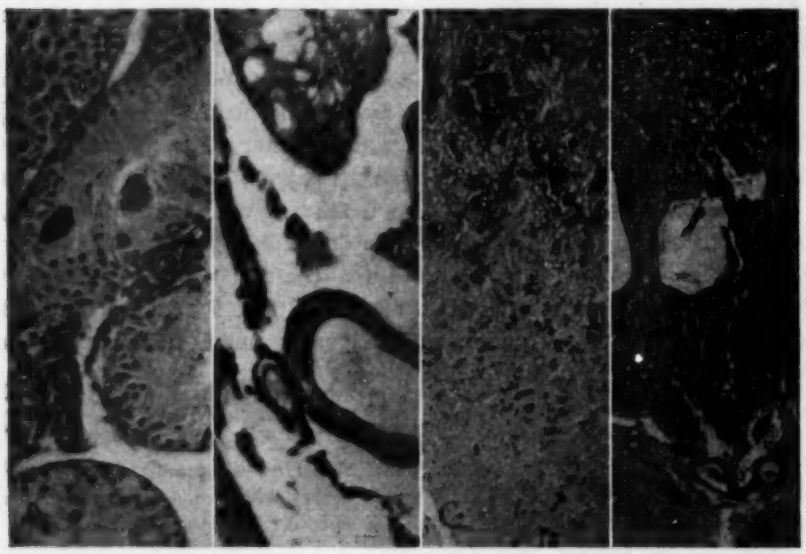

Fig. 1.—*A* and *B*, stages of testicular atrophy. *A*, the forty-two day stage shows giant cell formation, and *B*, the one hundred and forty-two days stage, shows complete degeneration. Hematoxylin and eosin; × 170. *C* and *D*, appearance of kidney in rather early (forty-two day) and quite late (ninety-one day) stages of deficiency. *C*, shows calcium deposited in the cortical intermediate zone and in the collecting tubules. Von Kossa stain; × 23. In *D* the renal pelvis (at the lower right) is intact; however, cortical cysts have been formed by intrarenal obstruction. Hematoxylin and eosin; × 15.

became a shell filled with fluid, consisting of a much thinned cortex with pelvic epithelium forming folds separated in part from the compressed cortical zone. At this stage, the ureters were of usual dimensions, and urine could be readily expressed from the bladder.

Histologic renal changes could be traced through a definite evolution, which was not always in strict chronologic order, though early changes were most

3. Kirkman, H.: Am. J. Anat. **73**:451, 1943.

frequent in periods of short deficiency, while only advanced lesions were seen after long periods of the diet. This is indicated graphically in figure 5.

The earliest change is the deposit of granular material, staining as calcium, in the lumen of the connecting and early portions of the collecting tubules (fig. 2). At this stage the concentration and the distribution of alkaline phosphatase are entirely normal; that is, the enzyme is in the brush border, in cuboidal cells of Bowman's capsule and near the afferent arteriole.[4] In fact, no histologic changes are identified in any part of the nephron. Shortly after this deposit has occurred, renal epithelial cells in this part of the tubule show degenerative changes; that is, they eventually desquamate, and the tubular lumen dilates. In ulcerated areas a granulomatous response appears now about the foreign material, composed of fibroblasts, lymphocytes and occasionally a giant cell of foreign body type. The progressive changes are shown in figures 3 and 4. This reaction, no doubt, completes the blockage begun by the calcareous deposits, for dilation of

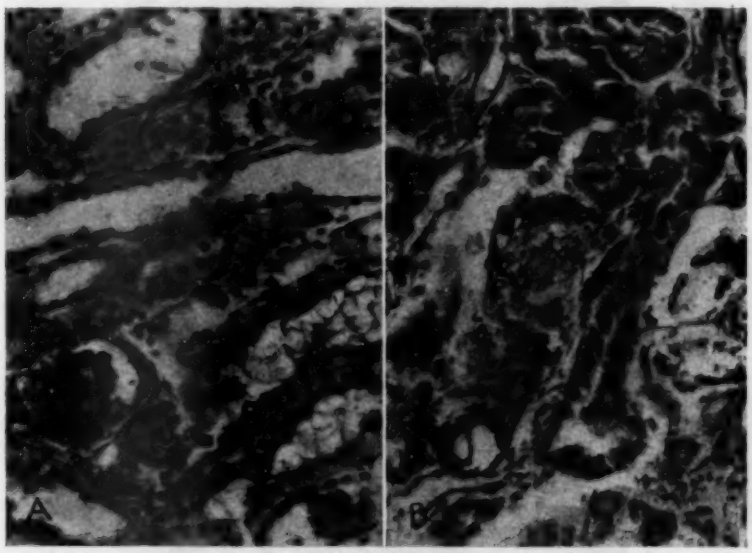

Fig. 2.—Stages 1 and 2 in the progression of the renal lesion. *A* (forty-two days) shows calcific casts in collecting tubules. Gomori's alkaline phosphatase stain; × 230. *B* (fifty-six days) shows interstitial and tubular reaction (stage 2). Hematoxylin and eosin; × 220.

portions of nephrons behind this region (that is, distal convoluted tubules) soon becomes marked. The proximal tubules remain intact very late in the process, often appearing separated by dilated distal loops and by interstitial fibrous and inflammatory tissue. At this stage alkaline phosphatase is still demonstrable in proximal convoluted loops. The process does not involve nephrons uniformly, and markedly altered units may be separated by single normal nephrons or groups of them. Late in the process the blockage of nephrons becomes widespread and perhaps more nearly complete, so that marked hydronephrosis, intrarenal in origin, results. The shell of cortical tissue, consisting of portions of nephrons proximal to the connecting tubules, shows a widespread granulomatous type of

4. Wachstein, M.: Arch. Path. **38**:297, 1944.

inflammatory response separating remaining tubules and glomeruli. These tubules and glomeruli are larger than normal—probably a compensatory hypertrophy of functioning units. Bowman's capsule is dilated, the result of late blockage. At this stage alkaline phosphatase has largely disappeared from the proximal tubular epithelium, indicating final functional interference.[5]

COMMENT

The foregoing description of the genesis of this lesion is in accord with known facts of renal tubular function. These rats, in chronic alkalosis, show as the earliest change—in fact, within a few hours [1]—

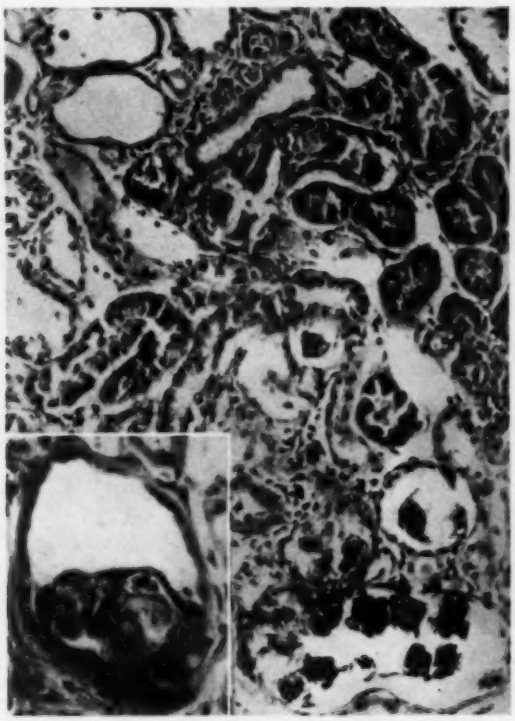

Fig. 3.—Stage 3: extensive granulomatous reaction with dilatation of distal tubules. A group of proximal convoluted tubules at the upper right is intact. Hematoxylin and eosin; × 170. The inset at the lower left shows a detail in the formation of a giant cell (× 450).

a marked drop in urinary excretion of chloride; even very early they excrete an alkaline urine. Since the distal tubule is the site of resorption of chloride [6] and of water [7] and the site of urinary acidifica-

5. Wilmer, H. A.: Arch. Path. **37**:227, 1944.

6. Walker, A. M.; Hudson, C. L.; Findlay, T., and Richards, A. N.: Am. J. Physiol. **118**:121, 1937.

(Footnotes continued on next page)

tion,[8] the abnormality is reflected in the urine in connecting and collecting tubules. Phosphates [7] likewise become elevated at this point. The alkalosis and the elevation of phosphates would tend to favor the precipitation of calcium salts. Similar though much less extensive changes are reported in cases of human alkalosis,[9] probably occurring only with associated dehydration. Hydronephrosis due to long administration of alkali in rats has likewise been reported.[10]

A somewhat similar histologic reaction has been observed as a response to necrosis of renal tubules in dietary serine damage,[11] a similar cellular response to a different injury. However, in the experiment reported here the fact that the normal histologic character and the normal distribution of alkaline phosphatase persists in the proximal

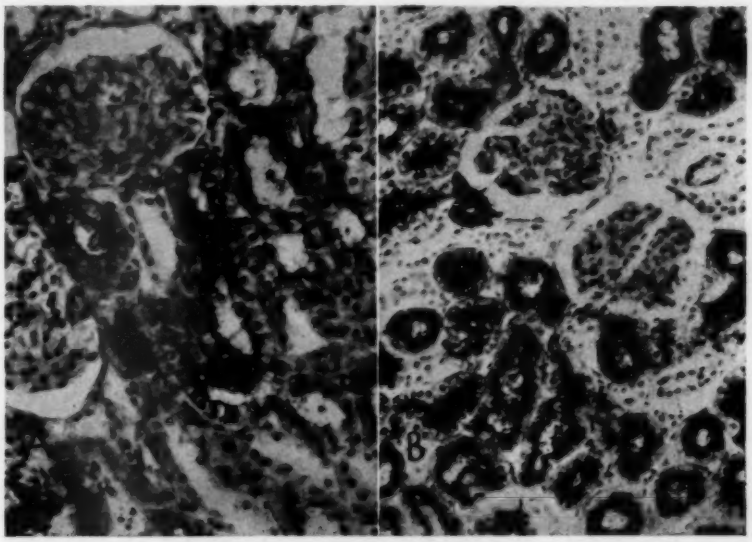

Fig. 4.—Distribution of alkaline phosphatase late in the process. *A*, stage 4, shows ragged alkaline phosphatase in a group of proximal convoluted tubules with absence of phosphatase on the left. Gomori's alkaline phosphatase stain, × 225. *B*, control at forty-two days, shows normal distribution of alkaline phosphatase. Gomori's alkaline phosphatase stain; × 170.

7. Walker, A. M., and Hudson, C. L.: Am. J. Physiol. **118**:167, 1937.

8. Montgomery, H., and Pierce, J. A.: Am. J. Physiol. **118**:144, 1937. Pitts, R. F.: Science **102**:49 and 81, 1945.

9. Kirsner, J. B.; Palmer, W. L., and Humphreys, E. M.: Arch. Path. **35**:207, 1943.

10. Addis, T.; MacKay, E. M., and MacKay, L. L.: J. Biol. Chem. **71**:157, 1926.

11. Morehead, R. P.; Fishman, W. H., and Artom, C.: Am. J. Path. **21**:803, 1945; **22**:385, 1946.

tubules until very late in the process indicates that the injury occurs by retrograde blockage, producing hydronephrosis, rather than by early degeneration and desquamation of cellular debris. The latter reaction occurs in heavy metal poisoning,[12] in which changes in alkaline phosphatase occur early and much of this material appears in the proximal tubular luminal debris. In fact, here the sequence of changes in the concentration of alkaline phosphatase is like that described in hydronephrosis due to ureteral ligation.[5]

It might be suggested that primary alterations of the distal convoluted tubules, occurring in somewhat the same manner as those described of spontaneous occurrence [13] but here produced by chemical aberrations, might be expected, since the brunt of the urinary chemical

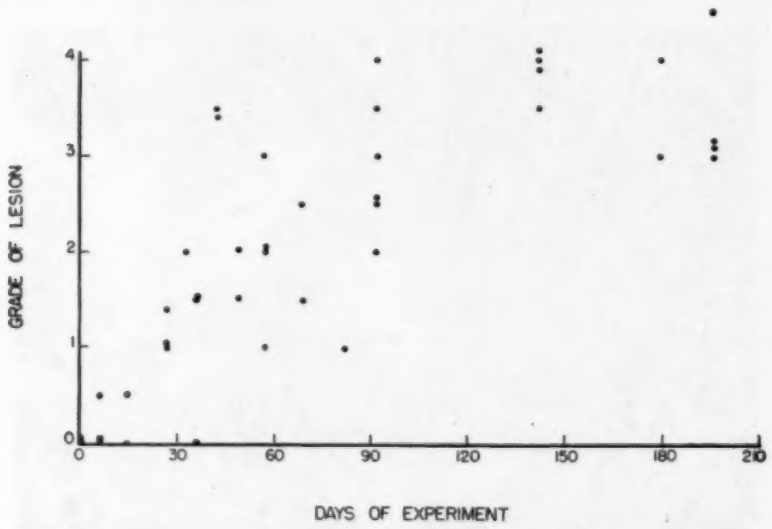

Fig. 5.—Progression of the lesion as influenced by duration of deficiency:

Grade 1. Deposition of calcium in connecting and collecting tubules.

Grade 2. The same as grade 1 with the addition of a tubular and interstitial granulomatous reaction.

Grade 3. The same as grade 2 with the addition of dilatation of distal convoluted tubules.

Grade 4. The same as grade 3 with extensive intrarenal hydronephrosis.

The control rats showed no renal changes.

abnormality is borne by these units. However, here the obstructive flattening of epithelium precedes any idiopathic histologic change, so that blocking from below better explains the lesion. Since MacNider found this change in old dogs, perhaps in older rats a primary change might occur in distal convoluted tubules.

12. Hepler, O. E.; Gurley, H., and Simonds, J. P.: Arch. Path. **39**:133, 1945.

13. MacNider, W. deB.: Proc. Soc. Exper. Biol. & Med. **55**:226, 1944.

The lack of complete chronologic regularity in the development of the lesion is to be expected, since other factors, notably the intake of water, would markedly influence the rate of deposition of calcium, dilute urine tending to delay the onset of heavy precipitation. There is, however, a fair degree of regularity in the development of late lesions, which occur only after many weeks of deficiency. So, although there may be variation in the time of appearance of the lesions, all rats suffer some involvement, which then progresses (fig. 5).

SUMMARY

A renal lesion uniformly develops in rats maintained on a chloride-deficient diet. Early in the process calcium is precipitated in the lumens of collecting tubules, with consequent blocking and hydronephrosis. A granulomatous inflammatory response is a characteristic early reaction to the foreign material and to the degenerating tubular epithelium. Chronic alkalosis is suggested as the basis of the precipitation of calcium.

ANGIOMATOID FORMATIONS IN THE GENITAL ORGANS WITH AND WITHOUT TUMOR FORMATION

ROBERT P. MOREHEAD, M.D.
WINSTON-SALEM, N. C.

IN RECENT years a group of neoplasms have been noted in the genital tract which possess an unusual but characteristic morphology. They have occurred most frequently in the epididymis and the testicular tunics, although similar lesions have been found in the uterus and the fallopian tubes. Essentially, they are composed of irregular islands and columns of spherical or oval cells displaying different degrees of vacuolation (fig. 1). Coalescence of these vacuolated cells results in the formation of spaces which are lined by cells resembling endothelium and occasionally by cells which have assumed epithelial characteristics (fig. 2). In some cases the vacuolated cells constitute the major portion of the lesion; in others they occur singly or in small groups between bundles of fibromuscular tissue (fig. 3), which not infrequently shows varying degrees of sclerosis and hyalinization (fig. 4). Another feature of these tumors is the presence of a large number of cells resembling lymphocytes, which in some instances are collected into nodules (fig. 5). These cells and those showing vacuolation constitute the characteristic features of tumors of this group.

To facilitate the description of the lesions and for reasons given later, they will hereafter be referred to in this paper as angiomatoid.

ANGIOMATOID FORMATIONS IN THE EPIDIDYMIS AND THE TESTICULAR TUNICS

Angiomatoid tumors arising in these structures have been described in the literature under a variety of names: "mixed leiomyoma and lymphangioma," [1] "lymphangioma," [2] "mesothelioma," [3] "adenoma," [4]

From the Department of Pathology, Bowman Gray School of Medicine of Wake Forest College.

1. (*a*) Halpert, B.: J. Urol. **45**:536, 1941. (*b*) Malisoff, S., and Helpern, M.: ibid. **50**:104, 1943.

2. Charache, H.: Urol. & Cutan. Rev. **43**:663, 1939. Foged, J.: Zentralbl. f. Chir. **66**:1402, 1939; Ugesk. f. læger **101**:806, 1939. Nakamura, Y.: Mitt. a. d. med. Akad. zu Kioto **26**:812, 1939.

3. (*a*) Evans, N.: J. Urol. **50**:249, 1943. (*b*) Masson, P.; Riopelle, J. L., and Simard, L. C.: Rev. canad. de biol. **1**:720, 1942.

4. (*a*) Blumer, C. E. M., and Edwards, J. L.: Brit. J. Surg. **29**:263, 1941. (*b*) Gordon-Taylor, G., and Ommaney-Davis, C.: ibid. **29**:260, 1941.

and "low grade adenocarcinoma."[5] Recently the noncommittal term "adenomatoid tumor" has been suggested.[6]

Most of the patients with these lesions have complained of no signs or symptoms other than the presence of an intrascrotal tumor. The neoplasms have varied from a few millimeters to 3 cm. in diameter and have been either well circumscribed or encapsulated. In general, they have presented the gross appearance of fibromyoma. The microscopic picture has varied somewhat, but the variations have been due for the most part to quantitative tissue differences rather than to pronounced qualitative alterations of the cells. The confusion in terminology has been in part due to these quantitative tissue variations. In an attempt to clarify the subject and to facilitate further description, these tumors are divided into several anatomic types.

Tumors Composed Predominantly of Fibromuscular Tissue but Containing Scattered Areas of Angiomatoid Tissue.—Neoplasms resembling fibromyoma but possessing angiomatoid areas have been described by Halpert[1a] and by Malisoff and Helpern[1b] under the name "mixed leiomyoma and lymphangioma." In tumors of this type the fibromuscular bundles constitute the greater portion of the neoplastic structure, the angiomatoid tissue being present only in small amounts.

Tumors Composed Predominantly of Angiomatoid Tissue but Containing Fibromuscular Tissue.—This type has composed the great majority of the neoplasms of the group under discussion which have been reported.[7] In this type the angiomatoid tissue is surrounded by connective tissue and smooth muscle, which show varying degrees of hyalinization.

Tumors Predominantly Angiomatoid and Showing Marked Sclerosis of the Fibromuscular Tissue.—No angiomatoid tumors which were characterized by hyalinization and sclerosis have been recorded in the literature. One of this type was, however, recently observed in this laboratory. Except for a pronounced degree of hyalinization and sclerosis of the fibromuscular tissue, it was similar to the type just described.

The patient was a 62 year old white man who was admitted to the hospital with a diagnosis of hypertensive cardiovascular-renal disease. On routine examination a small, hard nodule was discovered in the epididymis. At operation a small oval tumor was seen in the tail of the gland, and the neoplasm did not appear to be attached to the testicle proper. The entire epididymis was removed. Examination of the tumor showed a well circumscribed nodule possessing a definite capsule and measuring 1.5 by 1 cm. It was hard and composed of a pinkish gray tissue. Microscopically, it was seen to contain angiomatoid areas separated by a dense and abundant hyalinized tissue (fig. 6).

5. Thompson, G. J.: Surg., Gynec. & Obst. **62**:712, 1936.

6. Golden, A., and Ash, J. E.: Am. J. Path. **21**:63, 1945.

7. Evans.[3a] Masson and others.[3b] Blumer and Edwards.[4a] Gordon-Taylor and Ommaney-Davis.[4b] Thompson.[5] Golden and Ash.[6]

ANGIOMATOID FORMATIONS IN THE UTERUS

Angiomatoid tissue of the uterus has been described only in association with well developed fibromyoma. Most authors interested in the more common angiomatoid tumors of the epididymis have completely overlooked the similarity of these neoplasms to those which have

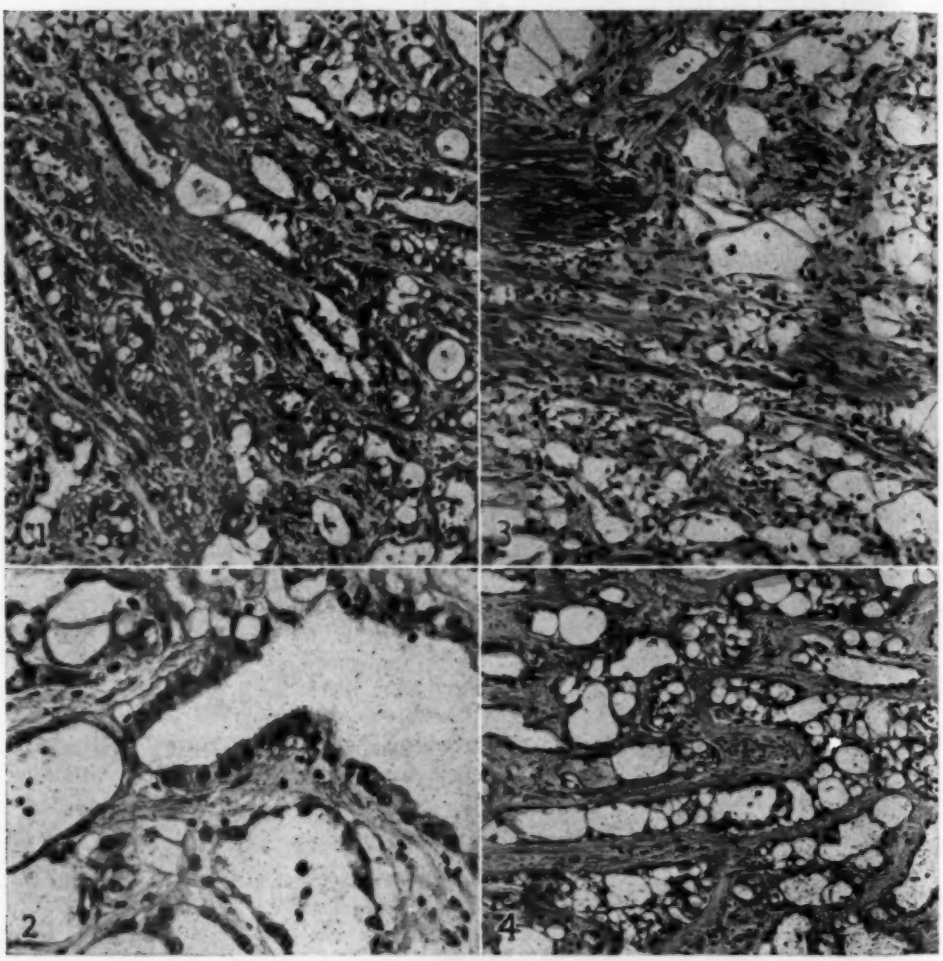

Fig. 1.—Angiomatoid tumor composed predominantly of angiomatoid tissue. Islands, columns and tubuloalveolar collections of cells showing various degrees of vacuolation and separated by connective tissue bundles which contain lymphocytes and smooth muscle cells. Some of the syncytial masses show beginning vacuole formation, while others have progressed to either the epithelial or the more advanced endothelial stage of differentiation. × 100.

Fig. 2.—The acinus to the right of the photomicrograph is lined by epithelium-like cells, while the wall of the one to the left is composed of endothelium. An intermediate stage is seen in the lower portion of the photograph. × 250.

Fig. 3.—Fibromyoma containing angiomatoid tissue. × 100.

Fig. 4.—An area of hyalinization and sclerosis in a tumor which is predominantly angiomatoid. The majority of the acini are lined by endothelium. × 100.

occurred in the uterus. Robert Meyer [8] has described as fibromyoma of the uterus a group of large submucous and intramural tumors which were composed predominantly of myomatous tissue but contained scattered angiomatoid areas. Meyer called the neoplasms "lymphangiectatic myomata." Recently Evans [9] has noted similar changes in a tumor diagnosed as fibromyoma which came under his observation. Structurally identical tumors have been described by Curtis [10] and also by Masson and associates.[3b] An excellent illustration of the neoplasms is to be found in Curtis' book.[10]

ANGIOMATOID FORMATIONS IN THE UTERINE TUBES

Few instances of angiomatoid formations in the uterine tubes have been recorded in the literature,[11] and prior to the report of Evans [9] all of these had been designated as lymphangioma. This author reported a "rounded tumor" 8 mm. in diameter on the wall of the uterine tube in a white woman 45 years of age and called it "mesothelioma." Microscopically, the lesion was seen to be composed primarily of angiomatoid tissue. It is worthy of note that the uterus contained multiple fibromyomatous tumors and a small, firm endometrial polyp. It may be significant that, with the exception of the cases reported by Strong,[11b] all angiomatoid nodules located in the uterine tube have been associated with myoma of the uterus. Recently cases of angiomatoid changes in the uterine tubes were reported by Golden and Ash.[6] An additional case which has come under my observation is reported.

A Negro woman 44 years of age was admitted to the hospital, complaining of a mass in the abdomen. At operation a pedunculated subserous tumor measuring 8 cm. in diameter was discovered, diagnosed as fibromyoma. The uterus was removed together with one fallopian tube and one ovary. Examination revealed, in addition to the uterine neoplasm, a roughly oval nodule 8 mm. in its greatest dimension and occupying the greater portion of the wall of the uterine tube. The nodule was well circumscribed but not encapsulated and was composed of angiomatoid tissue which extended from the serosa to the epithelial lining of the organ (fig. 7).

ANGIOMATOID FORMATIONS IN THE OVARIES

Angiomatoid changes in the ovaries have not heretofore been described. A recent case observed in this laboratory therefore deserves special consideration.

A white woman 26 years of age was operated on in August 1943, and the left fallopian tube and ovary were removed. The ovary had been almost com-

8. Meyer, R., in Stoeckel, W.: Handbuch der Gynäkologie, ed. 3, Munich, J. F. Bergmann, 1930, vol. 6, p. 237.

9. Evans, N.: Am. J. Path. **19**:461, 1943.

10. Curtis, A. H.: A Textbook of Gynecology, ed. 4, Philadelphia, W. B. Saunders Company, 1942.

11. (*a*) Leighton, A.: Am. J. Obst. **65**:573, 1912. (*b*) Strong, L. W.: Surg., Gynec. & Obst. **39**:318, 1924. (*c*) Masson and others.[3b]

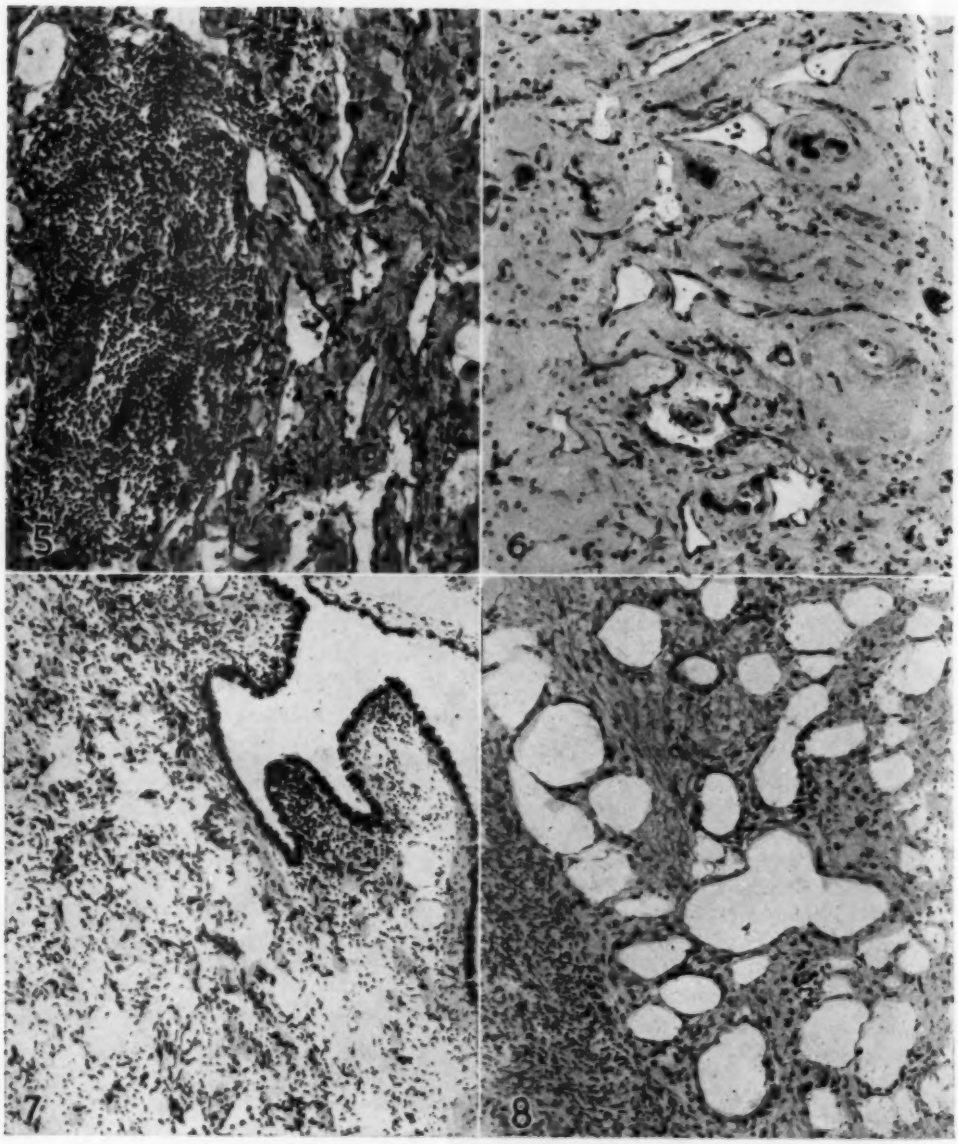

Fig. 5.—Large collections of lymphocytes in a sclerosed angiomatoid tumor. × 100.

Fig. 6.—Angiomatoid tumor of the epididymis characterized by marked hyalinization and sclerosis. × 100.

Fig. 7.—Angiomatoid tumor of the uterine tube. In the gross specimen the neoplasm appeared to be circumscribed, but note that the angiomatoid changes extended to the epithelial lining of the organ. Both endothelial-lined spaces and collections of lymphocytes are seen. × 100.

Fig. 8.—Angiomatoid tissue on the surface of the ovary. The angiomatoid tissue appears to be arising directly from the cortex of the organ. × 100.

pletely replaced by a cystic tumor which, after fixation in solution of formaldehyde, measured 6 cm. in diameter. The cyst was filled with a clear serous fluid, and a definite epithelial lining could not be demonstrated. No lesion was found in the fallopian tube. The patient made an uneventful recovery, but some time later she began to have abdominal pain. She was again operated on in February 1945, at which time the right ovary was removed. The organ had been almost completely replaced by small cysts containing either clear or bloody fluid and measuring as much as 1.5 cm. in diameter. The surface of the ovary was irregular and roughened. Microscopic study revealed that the cortex of the organ had been irregularly replaced by angiomatoid tissue. In some instances this tissue extended to the medulla, while in others it formed irregular accumulations on the surface (fig. 8). The germinal epithelial cells were prominent and at times were so arranged as to form adenomatoid structures (fig. 9). These, however, showed little anatomic similarity to the angiomatoid areas, and it was evident that the abnormal angiomatoid proliferations originated within the cortex and not from the germinal epithelium of the ovary. It should be emphasized that these changes occurred throughout the organ and that no circumscribed tumor formations were present.

OBSERVATIONS REGARDING THE ORIGIN AND DEVELOPMENT OF ANGIOMATOID TISSUE IN THE GENITAL TRACT

In their early development angiomatoid changes in the genital tract are confined for the most part to the connective tissue in the immediate vicinity of blood vessels, although they occur to a lesser degree within the substance of the fibromuscular tissue (fig. 10). The cells which compose this tissue most frequently appear as a syncytium (fig. 1), although they are also found singly or collected into small groups. The nuclei are oval and show a coarse reticular network of chromatin. Each possesses a prominent nucleolus and is surrounded by a moderate amount of eosinophilic cytoplasm. In many instances intracytoplasmic vacuoles appear within the more centrally placed cells of the syncytial masses. These in turn coalesce with vacuoles of adjacent cells and this coalescence results in the formation of glandlike lumens. The cells located at the periphery of the syncytium assume epithelial characteristics, while the nuclei of the more centrally placed cells shrink, become hyperchromatic and attain structural features similar to those of the mononuclear cells of the circulating blood.

During the process of luminal formation, and in some instances after it has become complete, vacuoles appear in the more peripherally placed cells of the syncytium (fig. 11). These vacuoles coalesce, and the nuclei stain more intensively with hematoxylin. The cellular changes observed thus far are similar to those noted in the more centrally placed cells of the syncytial masses. At this point, however, all of the peripherally placed cells do not proceed to form lymphocytes, some of them assuming structural characteristics similar to those of endothelium (fig. 12). Since no basement membrane surrounds the syncytium, the mononuclear cells readily make their way into the

adjacent tissues. The resultant structures are remarkably similar to lymph vessels which are surrounded by a scattering of lymphocytes.

Although in the majority of instances the angiomatoid cells appear in fairly large groups, it must be remembered that they are also seen singly or in small collections. In these instances it appears that vacuolation is followed by the formation of structures resembling lymph capillaries without the intermediary changes seen in the cells of the

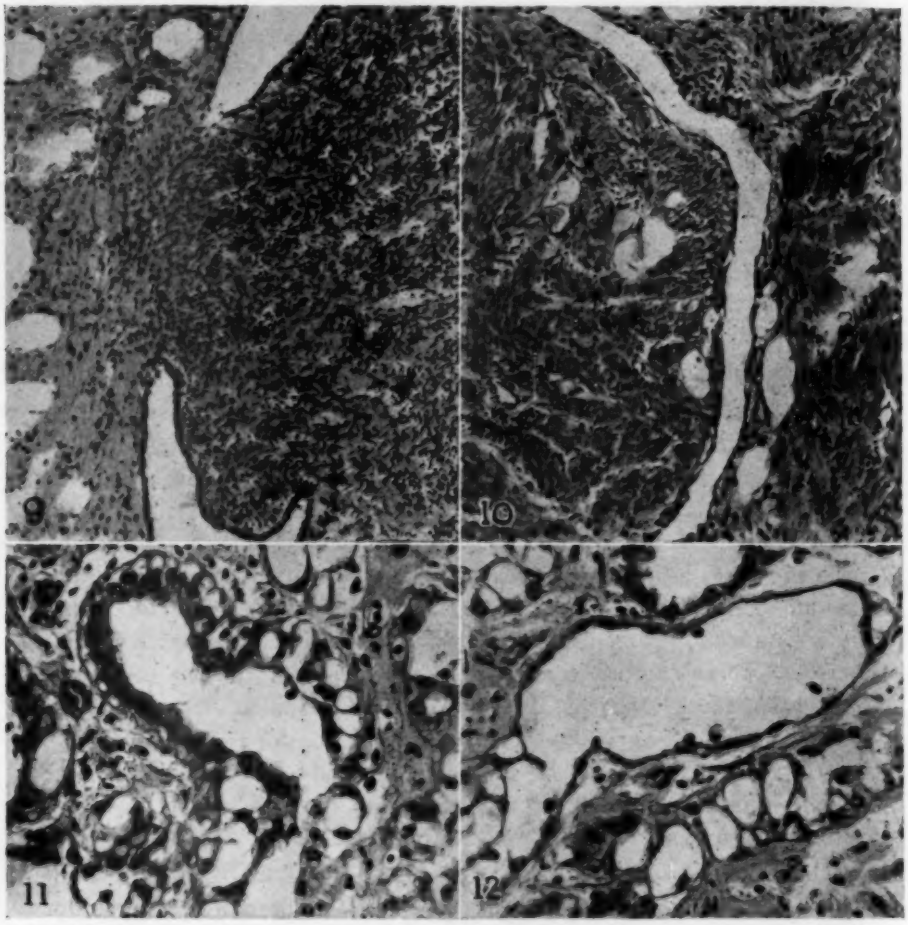

Fig. 9.—Angiomatoid tissue on the surface of the ovary. The germinal epithelium is prominent but apparently plays no part in the formation of the angiomatoid tissue. × 100.

Fig. 10.—Early angiomatoid changes in the wall of a vessel. Both angiomatoid spaces and collections of lymphocytes are seen. Isolated angiomatoid spaces are also present in the fibromuscular bundles. × 100.

Fig. 11.—Vacuolation of the peripherally placed epithelial cells resulting in the formation of angiomatoid structures and isolated lymphocytes. × 250.

Fig. 12.—An endothelium-lined channel. Note lymphocytes in the lumen and also in the wall. One mononuclear cell has a well defined rim of cytoplasm. × 250.

syncytial masses. Further, in many instances lymphocytes appear to arise singly or in groups directly from the mesenchyme.

The mode of development of these angiomatoid lesions suggests a histogenetic relationship to the formation of the vascular system. Embryonic tissue destined to form vascular channels first appears in the embryo as solid areas of cells which are called blood islands. Tiny vacuoles appear within these mesenchymal cells and rapidly coalesce, forming spaces. In this manner the solid areas are hollowed out, the more central cells becoming the earliest blood cells and the more peripheral ones assuming the characteristics of endothelium.[12] Prior to the formation of well developed endothelial cells, however, the peripheral cells show at one stage of the process structural characteristics suggesting epithelium. A striking similarity is seen, therefore, between the successive stages in the embryonic development of vessels and the formation of angiomatoid tissue.

SUMMARY

From the data presented it is evident that the lesions under consideration are composed primarily of two structural units, namely, (1) fibromuscular tissue of the type which ordinarily composes myoma and (2) groups of cells which are predominantly angiomatoid in arrangement and are intermingled with cells structurally resembling small lymphocytes. The majority of the tumors of this group which have occurred in the epididymis and the testicular tunics have been predominantly angiomatoid in appearance, although tumors described as myoma containing areas of angiomatoid tissue have been recorded. The latter type of neoplasm is the rule in the uterus, and the type which is predominantly angiomatoid has not been described in this organ. The angiomatoid nodules which have occurred in the uterine tubes have been small and have not possessed a definite capsule. Absence of a capsule is, however, to be expected, since many neoplasms—for example, myoma—do not acquire a capsule until they have reached a considerable size. The ovarian lesions seen in the case reported are of special interest, since they occurred as multiple foci and did not produce a definite tumor.

A detailed study of the available cases of angiomatoid tumor of the genital tract suggests that the sequence of events in the development of the neoplasm is similar to the formation of vascular channels and lymphoid cells in the embryo. These data strongly support the hypothesis that angiomatoid tissue is derived from mesenchymal cells which make imperfect attempts at the formation of lymph vessels and lymphocytes.

NOTE.—Drs. A. H. Curtis, C. H. MacKay and G. B. Adams gave me permission to examine their material and to incorporate it into this study.

12. Arey, L. B.: Developmental Anatomy, ed. 3, Philadelphia, W. B. Saunders Company, 1937.

HEPAR LOBATUM

Clinical Significance of the Anatomic Changes

DOUGLAS SYMMERS, M.D.
General Director of Laboratories, Department of Hospitals, City of New York
AND
DAVID M. SPAIN, M.D.
Assistant Pathologist, Bellevue Hospital
NEW YORK

THAT form of syphilitic cirrhosis of the liver known as hepar lobatum is often attended by symptoms and signs that are identical with those of Laennec's atrophic cirrhosis of the liver, especially in those cases in which the same mechanical factors prevail, such as the mechanisms that produce jaundice, ascites and esophageal varices. In other respects the two diseases may be distinguished one from the other only when it is possible to establish the syphilitic nature of the former and the absence of syphilis in the latter. Anatomically, hepar lobatum is characterized by a greater or less degree of deformity of the liver in the form of coarse and irregularly distributed lobulations due to the overgrowth of connective tissue. The latter is arranged around large groups of lobules and represents either the retracted scars of healed gummas or a chronic productive inflammatory process arising without the intervention of focal granulomas, or both. The surface of the lobulated areas is smooth. The incidence of hepar lobatum is indicated by the fact that the lesion was encountered 50 times in 314 cases of late acquired syphilis occurring among 4,880 necropsies at Bellevue Hospital, or in 16 per cent.[1] By this we do not mean to imply, of course, that hepar lobatum is susceptible of diagnosis in 16 per cent of all patients with late acquired syphilis. On the contrary, hepar lobatum may cause no symptoms or signs by which it could even be suspected during life.

Over a period of thirty years hepar lobatum was encountered 102 times among 23,792 necropsies at Bellevue Hospital. According to the clinical records of 28 cases that were available for analysis, the lesion occurred 23 times in males and 5 times in females; 24 patients were of the white race and 4 were Negroes. The average age was 38.5 years; the youngest patient was 19 and the oldest 80. Six patients admitted

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From the Laboratories of Pathology, Bellevue Hospital.

1. Symmers, D.: J. A. M. A. **66**:1457, 1916.

excessive use of alcohol. The diagnosis of syphilitic cirrhosis of the liver was made during life in 3 cases, and the condition was suspected in 1. In 18 cases the liver was palpable below the right costal slope for distances varying from 2 to 12 cm.; in 6 instances the liver was nodular, and in 10 the organ was tender. The spleen was palpable in 13 cases. Jaundice occurred in 8 cases, ascites in 18 and hematemesis in 7. In 12 cases fever was present. The temperature was irregular, varying between 100 and 106 F. The Wassermann reaction was strongly positive in 10. Syphilitic lesions, such as cutaneous gumma, fibrosis of the testicles and penile scar, were noted in 10 cases. From these facts it is apparent that the clinical diagnosis of hepar lobatum depends almost exclusively on such physical signs as jaundice, ascites and residual lesions of syphilis occurring elsewhere and that symptoms are few and of comparatively little importance. The paucity of symptoms

Incidence of Hepar Lobatum by Decades of Life

Age	Number of Cases	Percentage
9	1	0.9
10-20	3	2.9
21-30	8	7.9
31-40	27	26.5
41-50	29	28.7
51-60	21	20.8
61-70	11	10.9
71-80	2	1.9

and the relative frequency of physical signs are evident in MacCrae and Caven's analysis of the changes in 100 cases of hepar lobatum which were studied from the purely clinical point of view.[2]

INCIDENCE

The incidence of hepar lobatum by decades of life in 102 cases is given in the accompanying table.

In patients between 30 and 50 years there were 56 cases (54.9 per cent). The lesion, therefore, is one of youth or of comparative youth.

The lesion occurred 83 times in white persons and 19 times in Negroes, a ratio of 4.4 to 1. The proportion of white to Negro patients admitted to Bellevue Hospital is 4 to 1. There were 71 males and 31 females, a ratio of 2.3 to 1. The proportion of male to female patients admitted to Bellevue Hospital is 1.3 to 1. The disease, therefore, is commoner in males than in females and more common in white people than in Negroes.

2. MacCrae, T., and Caven, W. R.: Am. J. M. Sc. **172**:781, 1926.

In 1927 an abrupt decline occurred in the number of cases of hepar lobatum encountered in necropsies at Bellevue Hospital. In view of the fact that about seventeen years earlier preparations of arsenic came into more or less general use in the treatment of syphilis, it seems reasonable to assume that the decline was due, at least in part, to the effects of therapy.

POSTMORTEM OBSERVATIONS

In 102 cases of hepar lobatum the following changes were noted at necropsy:

Jaundice occurred in 35 cases (34 per cent); it was slight in 8, moderate in 10 and intense in 17.

Ascites occurred in 32 cases (31 per cent).

Esophageal varices were noted in 15 cases (15 per cent), and in all of them rupture had occurred during life. Unruptured varices, if present, were not recorded.

The state of nutrition was recorded in 40 cases. In 8 cases it was described as "poor" and in 20 as "good"; in 12 cases the subjects were said to be emaciated.

Miscellaneous associated lesions of syphilis were noted in 68 cases (67 per cent). In order of their frequency they occurred as follows: syphilitic aortitis in 21; chronic interstitial syphilitic splenitis in 18; fibrosis of testicles in 14—unilateral in 3, bilateral in 11; changes in the bony system in 7; cerebrospinal syphilis in 3; smooth indurative atrophy of the base of the tongue in 2; gumma of lymph nodes, tracheitis and congenital syphilitic pancreatitis each in 1.

Liver.—In 37 cases (36 per cent) the liver was coarsely nodular, and in 4 of these the edge of the organ projected beneath the right costal margin, reaching in 2 as low as the level of the umbilicus. In 2 cases the liver was the site of amyloid deposits. In 53 cases the average weight of the liver was 1,556 Gm., a weight which approximates the normal. The smallest liver weighed 608 Gm. and the heaviest 3,450 Gm. Solitary gumma was noted in the liver in 7 cases and multiple gumma in 12; in only 3 of these 19 cases did a gumma project above the upper surface of the liver and appear to invite detection during life.

Spleen.—In 47 cases of hepar lobatum the spleen was described as "normal in size," "slightly enlarged," moderately enlarged," or "considerably enlarged" at necropsy. In an additional 55 cases the average weight of the spleen was 538 Gm., or 338 Gm. in excess of the extreme normal limit of 200 Gm. The smallest spleen weighed 24 Gm. and occurred in a 9 year old subject with congenital syphilis. Among adults the smallest spleen weiged 60 Gm. and the largest 1,980 Gm. In 18 of the 102 cases of hepar lobatum the spleen showed the changes

incident to chronic interstitial syphilitic splenitis, and in 3 cases deposits of amyloid were present.

There is a form of splenomegaly which occurs in persons with late acquired syphilis, perhaps exclusively, that is attended by pinhead-sized, ochre-colored bodies consisting microscopically of thickened and hyalinized central arteries with mineralization of their fibromuscular and elastic coats, together with mineral-free hyaline deposits in and around neighboring venules, as well as periarterial hemorrhagic extravasations. It seems that up to 1919 only 9 cases had been described in medical literature—1 each by Simonds,[3] Sprunt[4] and Marini[5] and 6 by Symmers, Gettler and Johnson[6]; 2 additional cases have since been recorded in the necropsy reports of Bellevue Hospital and 1 case at Goldwater Memorial Hospital. The spleens were enormously enlarged, weighing 1,000, 1,280, 775, 1,900, 3,410, 1,275, 1,050, 1,040, 1,150, 1,020 and 1,030 Gm., an average of 1,357 Gm., or 1,157 Gm. above the high normal weight of the spleen in adults. In 1 case the weight was not recorded, but the spleen was described as "three times larger than normal." In this form of splenomegaly it appears that hemorrhage is followed by disintegration of hemoglobin, with iron compounds being deposited in the hyalinized arterial coats, and that the circulation is impaired in such manner as to permit escape of serum, with the precipitation of calcium in fibers that are prepared for its reception as a result of previous deposition of iron. Also, salts of silica and phosphorus are present in increased quantities, the former accounting, apparently, for the ochre color of the deposits in the substance of the spleen. In the 6 cases recorded by Symmers, Gettler and Johnson and in the 3 cases since encountered at Bellevue and Goldwater Memorial hospitals the patients all had syphilitic cirrhosis of the liver or syphilis of the liver and other organs, including fibrosis of the testicles, rupia and like residua.

SUMMARY

From the foregoing observations it is evident that in a certain number of instances hepar lobatum is attended by anatomic changes which are detectable during life and that the incidence of the lesion is such as to warrant a search for it in all cases of late acquired and late congenital syphilis. A history of syphilis and a positive Wassermann reaction or other serologic evidence are important, but signs in the skin or in the visible mucous membranes, fibrotic lesions of the testicle,

3. Simonds, J. P.: J. Infect. Dis. **5**:23, 1908.

4. Sprunt, T. P.: J. Exper. Med. **14**:59, 1911.

5. Marini, G.: Arch. per le sc. med. **26**:105, 1902.

6. Symmers, D.; Gettler, A. O., and Johnson, W. M.: Surg., Gynec. & Obst. **28**:58, 1919.

changes in the bony system, penile scars and the like, or jaundice associated with an enlarged, firm spleen, with or without ascites, should direct attention to the liver as the possible seat of syphilitic cirrhosis. Finally, in approaching the clinical diagnosis of hepar lobatum it would seem, first, that confirmatory evidence should be sought in the form of response to treatment with iodides or other appropriate therapy and, second, that consideration should be given to the advisability of investigating the changes in the liver by the process of biopsy.

BIREFRINGENCE IN TISSUES

A. L. LICHTMAN, M.D.
AND
JOHN R. McDONALD, M.D.
ROCHESTER, MINN.

ALTHOUGH students of the finer structure of matter have used the polarizing microscope extensively,[1] there has been little application of the polarizing technic in pathology. This is surprising in view of the ease with which a polarizer and analyzer can be added to an ordinary microscope. Many details not visible in ordinary light are brought into view. Routine methods of preparing sections cause solution of lipids and overshadow inert particles. The double refraction of light by biologic substances is a reflection of the fundamental structure of tissues.

Schmitt [1] distinguished three types of birefringence in tissues.

The first is crystalline birefringence, caused by the regular anisotropic array of the molecules in the substance. It is inherent, and is not altered by changes in the surrounding mediums. Protein, lipid and carbohydrate components show inherent positive uniaxial birefringence, whereas nucleic acid derivatives show inherent negative uniaxial birefringence.

The second type is stream or photoelastic birefringence which results from molecular orientation by external deforming forces. This permits display of birefringence by isotropic solids or liquids. Stream birefringence can be elicited by stirring anisodiametric micelles. The paracrystalline state of tobacco mosaic virus was indicated by its positive birefringence.[2] Knowledge of contractility was advanced by the demonstration of rotation of molecular links without change in primary valency angles of long chain molecules of myosin and elastoidin.[3]

The third type is form birefringence, produced by preferential orientation of nonspherical units in a medium of different refractive index. Therefore, it changes with the refractive index of the surrounding mediums and has a zero point. Positive fiber birefringence signifies parallel adlineation of rodlets in the long axis of the fiber. In negative birefringence, platelets, leaflets or disks are oriented perpendicular to

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From the Division of Surgery (Dr. Lichtman) and the Section on Surgical Pathology, Mayo Clinic.

1. Schmitt, F. O.: Physiol. Rev. **19**:270, 1939.
2. Lauffer, M. A., and Stanley, W. M.: J. Biol. Chem. **123**:507, 1938.
3. Astbury, W. T., and Dickinson, S.: Nature, London **135**:95 and 765, 1935. Schmitt.[1]

the long axis of the fiber. Inherent and form birefringence may be found in the same fiber. Apparent negative birefringence can be produced in a fiber by perpendicular orientation of an otherwise positive lipid component. Fibrous structures display linear symmetry, whereas cellular membranes and films show planar symmetry. Anisotropic granules may display radial symmetry, as evidenced by a polarization (maltese) cross in polarized light.

BIREFRINGENCE IN TISSUES

In examination of fresh frozen sections of tissue under polarized light, little alteration is seen in the physicochemical structure of the tissue. The molecular organization producing the refraction is fundamental in the function and the structure of those substances which are locomotive, conductive or supportive. This method of examination also serves as a check on artefacts produced by other methods of examination.

Nervous Tissue.—Recently, Witwer, Derbyshire and Corrigan [4] made a preliminary report on the use of polarized light in the study of tumors of the brain. The fresh myelin sheath exhibits positive uniaxial birefringence with the optical axis disposed radially.[5] There are concentric lamellas of lipid and neurokeratin protein. The long axes of the protein chains are situated parallel to the surface of the sheath, whereas the lipid molecules are radially oriented. The axon itself displays fiber birefringence. When a nerve is severed, the myelin lipids exhibit changes in polarized light in a few hours. With degeneration, planar asymmetry and anisotropic granules appear. The usual myelin stains will not reveal changes for days.

Muscle.—Birefringence in striated muscle has been recognized for many years.[6] It is positive with respect to the long axes of the fibers. The magnitude of birefringence is greatest in the A (or Q) disk and the Z disk (Krause's membrane). The I (or J) band is faintly birefringent. During contraction the A disk is reduced in thickness; in stretching it increases. The suggestion has been made that contraction is associated with reduced orientation in the A disk region. Examination of cardiac muscle from human beings, dogs and rats reveals similar birefringence. The intercalated bands are not birefringent. Smooth muscle from the same sources shows much less birefringence.

Collagenous Connective Tissue.—This type of tissue displays uniaxial positive birefringence.[1] There is an increase in the birefringence in embryonic fibrous tissue, in developing scar tissue and in areas associ-

4. Witwer, E. R.; Derbyshire, A. J., and Corrigan, K. E.: Radiology **41**:130, 1943.

5. Schmitt, F. O., and Bear, R. S.: Biol. Rev. **14**:27, 1939.

6. Engelmann, T. W.: Arch. f. d. ges. Physiol. **11**:432, 1875.

ated with chronic inflammation.[7] Fresh frozen sections of such tissue were subjected to incineration at 550 C. for one hour, so that ghost tracings of the tissue were produced. Comparison with similar sections from similar, normal, well established areas showed that there was an increase in birefringent crystals in the proliferating tissue. The silicon content of connective tissue is the highest of that of normal tissues. In the aforementioned sections there was an increase in silicate and calcium crystals. The factors of hydration and increased orientation were not measured.

The production of a characteristic type of fibrous tissue in dogs by subperitoneal injection of talc has been reported previously.[7] It was observed that the talc crystals tended to adlineate themselves with the long axes of the developing fibroblasts and the subsequent long axes of the collagen fibrils. Long chain anisotropic molecules create a field of force in which adjacent micelles are constrained to adlineate. The organization by orientation of anisotropic substances which support, protect or move organisms is a result of the asymmetry that produces birefringence. In short, asymmetry breeds asymmetry. Talc crystals in the presence of developing fibrous tissue act as compasses of the adlineating force.

The basket weave laminations found in fibrous nodules are a result of this force. Communicating bands may be seen between layers, permitting streaming. This is offered as an explanation of how large fibrous nodules may exist with little visible blood supply. Polarized light permits distinction of different types of connective tissue without special stains, for each type of fiber has a characteristic pattern.

Fatty Tissue.—Unmodified fat cells display few birefringent inclusions. In the presence of infection, or on exposure to air or to formaldehyde, birefringent specks are visible. Foam cells are emulsions in which the cytoplasm is in the diffuse phase. If the lipid is birefringent, the foam cell becomes a crystal mass containing myriads of brilliant jewels under polarized light. The droplets within a cell are all of the same size.

Bone.—Positive form birefringence originates from the collagenous matrix which orientates the apatite lamellas.[8] The collagen fibrils run roughly parallel and at right angles to the axis of the haversian canal. If the collagen is leached out, the birefringence is reduced, but residual orientation of the apatite micelles may be seen.

If calcium deposits from regions affected by inflammation or atheromatous plaques are ground up, flat hexagonal crystals may be seen. The

7. Lichtman, A. L.; McDonald, J. R.; Dixon, C. F., and Mann, F. C.: Surg., Gynec. & Obst., to be published.

8. Picken, L. E. R.: Biol. Rev. **15**:133, 1940.

birefringence is low, and the optical axis is perpendicular to the flat surfaces of the crystals. Granular material which stains blue with hematoxylin is not birefringent.

Hydroxyapatite, the form that calcium phosphate takes in teeth, shows negative intrinsic birefringence and positive structural birefringence. Cementum and dentin also are birefringent.

In the presence of gout, crystals of uric acid and amorphous sodium biurate are deposited, and they provoke a foreign body reaction. The marked birefringence of these crystals makes identification of them easy (fig. 1 *a*). Polarized light also permits positive identification of urea crystals.

Blood.—Polarized light of high intensity is necessary to bring out the birefringence of the protein laminas which envelop erythrocytes. Chylomicrons, which show so well under the dark field microscope, are not birefringent.

Chromosomes.—The double refraction in chromosomes results from changes in hydration of the chromatin. There are both form birefringence and intrinsic birefringence. The latter is negative uniaxial, resulting from the nucleic acid molecules arranged parallel to the long axes of the chromosomes.[8] Lines of stress may play a part in the birefringence of asters and spindles.

Skin and Appendages.—In conjunction with the electron microscope and roentgen ray diffraction, the spatial arrangement of the long chain protein molecules of keratin has been studied by polarized light analysis. Many practical applications have resulted from knowledge that was gained by studying the effect of stretching, contraction, supercontraction and heat on the protein chains.[8] Similar methods have been applied in study of the reversible extensibility in synthetic long chain polymers.

Hair, nail and horn exhibit positive uniaxial birefringence of great magnitude. The birefringence of the hair shaft is greatest in the keratinized spindle cells of the cuticle. Dehydration in the distal portion makes the birefringence more prominent. Information gained by inspection of hair under polarized light has attracted the attention of anthropologists, medicolegal experts and those interested in shampoos and permanent waving.

The degenerating keratin in epidermoid cysts loses its birefringence because of hydration, swelling and decay. Pearly bodies in squamous cell carcinoma are markedly birefringent. Nail shows birefringence, with its keratin chains running along the plane of the nail. Sebaceous gland cells show occasional birefringent inclusions.

Eye.—The collagen fibers of the sclera are markedly birefringent; the fibers of the cornea are less so. The optic axes of the fibers are parallel to the surface. In the substantia propria of the cornea there

are cross striations of the birefringent substance that is not collagen. Since the optic axes of these fibers are perpendicular to the surface of the cornea, they permit light to enter the optic globe without double

Fig. 1.—(*a*) Deposits of uric acid and amorphous sodium biurate found in gout; there is a marked foreign body reaction (× 60). (*b*) Birefringent crystals in the presence of thyroiditis, found in a colloid goiter. The wide distribution of the crystals suggests that they were factors in the production of the lymphocytic proliferation in this thyroid gland (× 60; partial extinction).

refraction. Where the laminas of the cornea were separated in cutting the sections, these cross striations were absent. We could find no discussion in the literature of the effect of the birefringence of the

cornea, or of what part the cross striations play in preventing it. The normal crystalline lens and the aqueous and the vitreous humor are optically isotropic. The retina, however, contains many structures which display double refraction. There are the myelin sheath and the neural axon, the surface of the erythrocyte and the rod and the cone. However, in the rod and the cone the optic axis is parallel to the long axis of the cell, and light can be absorbed without refraction. These interesting relationships warrant detailed study.

Thyroid Tissue.—The parenchymal cells contain birefringent specks. These were too small to identify. The aggregates increase in size in parenchymatous hyperplasia and after treatment with thiouracil. Normal colloid is not birefringent, but colloid of diseased glands shows birefringent crystals. In figure 1 *b* are shown the crystals in a colloid goiter. In regenerative hyperplasia cholesterol crystals and rosettes of fine acicular crystals are seen. Two cases were found in which the masses of crystals had provoked formation of pseudotubercles, so that the gland was first considered to be tuberculous (fig. 2 *a* and *b*). It was apparent that the epithelioid and lymphocytic infiltration in some thyroid glands was produced by a birefringent substance elaborated by the thyroid gland.

Lung.—Polarized light is useful in the study of the silicotic nodule. Particles between 0.5 and 3 microns do the most damage, obstructing the lymphatic mechanism of disposal. The laminated collagenous nodule is markedly birefringent, and although silica dust is visible in the vicinity, few particles are visible within its confines. However, if the section is incinerated, silica particles that were too small to be visualized are seen within the area of the nodule. Miners who have been exposed to silica dust for a long time also will be found to have silica in the liver and the spleen, for the particles can be transported to the blood stream. Asbestos, a birefringent silicate, produces a distinct variety of pneumonoconiosis in which the initial lesion is a cuff of fibrous tissue in a bronchiole. The direction of the progression of the lesion is opposite that followed by silicosis. Talc, another birefringent silicate, causes a self-limited granuloma without progressive fibrosis. In rare instances, discrete fibrous nodules may develop in the lungs of farmers and processors who are exposed to high concentrations of wheat dust for long periods. The cellulose in the wheat dust can be seen, since it is birefringent.

Breast.—In plasma cell mastitis, plasma cell and lymphocyte infiltration is found.[9] Pseudotubercles sometimes lead to an early impression that the condition present is tuberculosis. But polarized light will

9. Cromar, C. D. L., and Dockerty, M. B.: Proc. Staff Meet., Mayo Clin. **16**:775, 1941.

reveal that there are birefringent crystals which produced the characteristic picture. The lesion seems to stem from points where the walls of the dilated ducts have lost their continuity. In some cases the regional lymph nodes showed that some of the crystals had been transported. The crystals were common in the peripheral sinuses.

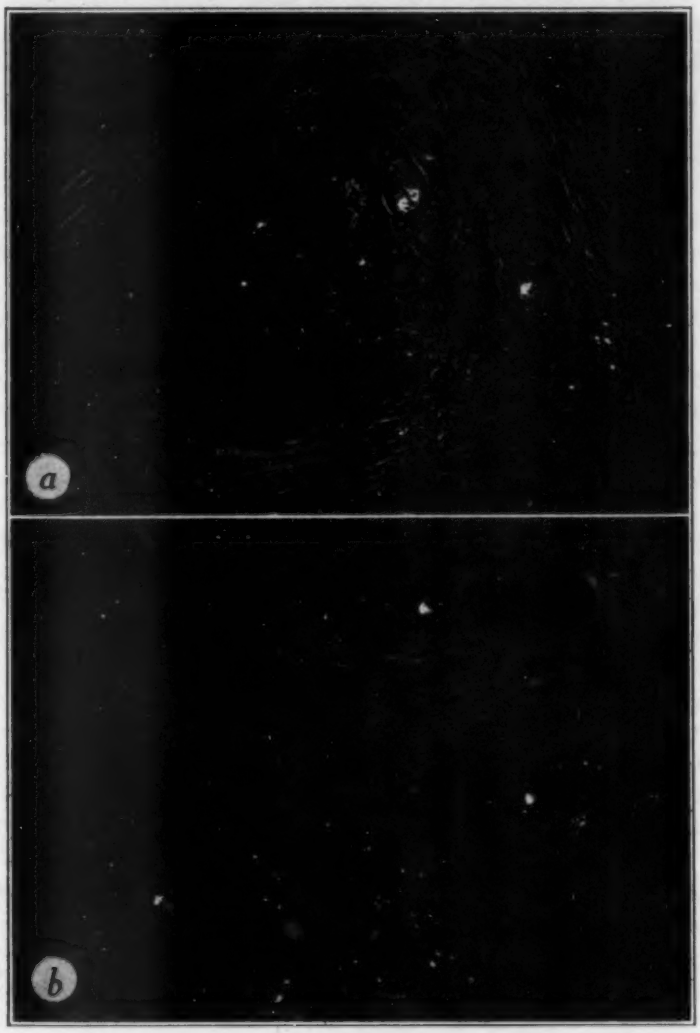

Fig. 2.—(*a*) Section of thyroid gland with foreign body reaction to cholesterol esters, which have exerted a foreign body pseudotubercle reaction so closely simulating tuberculosis that the gland was believed to exhibit noncaseous tuberculosis; there were well developed tubercles and extensive fibrosis (× 100, with polarizers at half extinction to show surrounding histologic aspects). (*b*) Another case in which the histopathologic aspects of the pseudotubercle response around birefringent crystals suggested the diagnosis of "tuberculosis of the thyroid gland" (× 40).

Liver.—Although the liver is the site of esterification of cholesterol, the polarizing microscope gives little evidence of this activity. A few birefringent specks are seen in the cells in the center of the hepatic lobule and in the Kupffer cells. This suggests that the cholesterol esters are present in the diffuse phase, and hence that there are no paracrystals. In the presence of cirrhosis of the liver the fibrous tissue is marked by its usual birefringence.

Gallbladder.—In cholesterosis or strawberry gallbladder, the enlarged villi are filled with lipid. Some authors have suggested that these break off and form seeds for the formation of cholesterol stones. The masses of amorphous fatty acids are faintly birefringent. Typical cholesterol crystals are abundant. Distinct paracrystals of cholesterol esters are infrequent. They are found only in those gallbladders that exhibit the greatest degree of cholesterosis (fig. 3 *a*). The lipid masses provoke little reaction other than "storage" histiocytosis. But occasionally a gallbladder is seen in which cholesterol ester aggregates have produced a pseudotubercle response. In 1 such case the cholesterol esters had been transported to the hepatic lymph nodes and had produced a picture resembling that of noncaseous tuberculosis.

Gastrointestinal Tract and Peritoneal Cavity.—In 198 cases of so-called noncaseous tuberculosis of the ileum specimens were examined, and birefringent crystals were found to be related to the lesion in 49 cases. In 33 cases enough crystals were present to have caused the pseudotubercle reaction.[7] Where inflammation is present, the connective tissue shows increased birefringence. The action of talc in causing persistence of fecal fistulas and its effect when it is injected subserously into dogs have been reported previously.[10] Both talc and cholesterol esters may produce pseudotubercles in the peritoneum, so that the picture resembles tuberculous peritonitis. In 102 cases the nodules of the peritoneum were subjected to biopsy because tuberculosis was suspected, and in 6 cases the nodules showed talc granuloma, and in 5 cases cholesterol esters were demontrated to have been the cause of the pseudotubercle response.

Spleen.—Where there is an increase in the fibrous tissue of the spleen, it is clearly demarcated by its birefringence. One spleen was observed in which cholesterol esters had provoked a pseudotubercle response. In so-called sarcoidosis of the spleen, markedly birefringent asteroid bodies are present. The crystals have not been identified, but they seem to be the cause of the reaction.

Adrenal Gland.—The fasciculate zone of cortical cells exhibits myriads of birefringent spherites. The E compound, F-acetyl, corticosterone and desoxycorticosterone all are markedly birefringent.

10. Lichtman, A. L., and McDonald, J. R.: Surg., Gynec. & Obst. **78**:449, 1944.

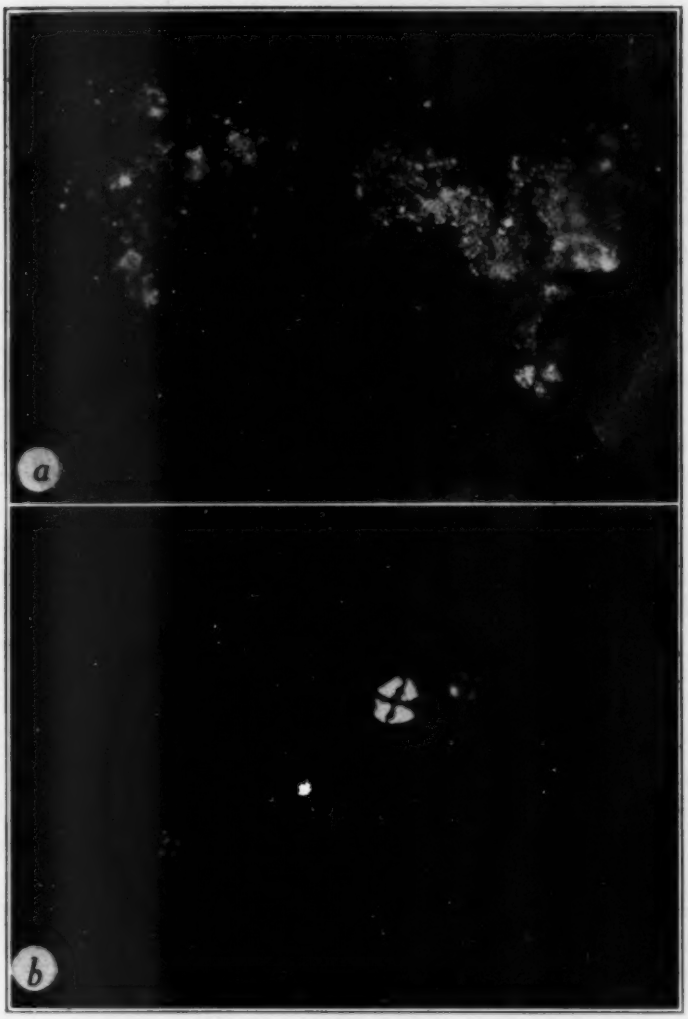

Fig. 3.—(*a*) Clubbed villi of a gallbladder, showing cholesterosis. This is a fresh frozen section seen under polarized light at half extinction. The very bright specks are liquid crystals of cholesterol ester; the maltese cross pattern is difficult to photograph, but it shows in some of the droplets. The remainder of the material is uncombined cholesterol and other lipids; when sloughed into the bile these masses conceivably may be seeds for the formation of crystal aggregates or stones (× 105; half extinction). (*b*) Photomicrograph, at total extinction, of liquid crystal cholesterol esters in the cells of the tubules of the kidney in the presence of so-called lipoid nephrosis; the three liquid crystals show the dark maltese cross formed by four quadrants of refracted light; minute droplets of anisotropic liquids show this polarization cross because of the symmetric radial orientation of the crystallite molecules contained in the droplet. As the physical state changes, an actual rosette of acicular crystals, such as that shown in figure 4, forms. During this transition the granule acquires a foreign body status. When the aforementioned paracrystallite is viewed by the addition of a selenite or gypsum red I crystal, the change in order of the colors in the right upper quadrant and the left lower quadrant identifies the positive birefringence of the cholesterol ester liquid crystal due to structural orientation (× 435; total extinction).

Conference with Dr. E. C. Kendall revealed that the amounts of cortical hormone present in the adrenal gland were not sufficient to permit visualization. The birefringent droplets in the adrenal gland, the ovary and the testis have prompted the suggestion that they are the substance utilized in elaboration of the steroid hormones. Doubt is cast on this by the fact that these droplets are present in organs in which no known steroid hormone is produced.

Kidney.—Paracrystalline (liquid crystal) droplets are seen in the tubules of the kidney and in the urine in the presence of lipoid nephrosis (fig. 3 *b*) and to a much less extent in some cases of glomerulonephritis. An attempt was made to study the deposition of cholesterol esters in the kidney. Dogs received a low protein diet, and their blood proteins were depleted by daily plasmapheresis. Hyperlipemia, hypercholesteremia, hypoproteinemia and albuminuria were marked, but cholesterol esters did not appear in the urine. At postmorten examination cholesterol ester droplets were not found in the kidney. The gastrointestinal tract was the site of multiple small ulcers. The experiment was repeated, with the addition of a single dose of 1 mg. per kilogram of uranium nitrate, given intravenously. Large numbers of cholesterol ester paracrystals were found in the urine, and at postmorten examination many polarization crosses were seen in the convoluted tubules and Henle loops of the kidney.

Prostate Gland.—Granulomatous prostatitis is characterized by an extensive infiltration of plasma cells, large pale mononuclear cells and foreign body giant cells, which replace the normal structure. It has been suggested that the lesion is caused by prostatic secretions that escape into the tissue.[11] Examination by polarized light reveals large numbers of fine acicular crystals closely related to the lesion. Staining of the sections with sudan III reveals that one type of crystal absorbs the dye, whereas the other type does not. The former seems to be fatty acid esters, and the latter, nucleatide or phosphatide complexes.

Testis and Ovary.—The interstitial cells of the testis and the corpus luteum cells of the ovary show birefringent inclusions. The relationship of these to the functional activity of the gonads is worthy of further study. Examination of ovarian tumors derived from the corpus luteum cells showed myriads of birefringent inclusions.

If a fresh motile human spermatozoon is examined, little can be seen when an ordinary intensity of light is employed. If a light of high intensity is used, or if the specimen is dried or treated with alcohol, birefringence can be seen in the pellicle tip of the head and in the fibrils in the tail.

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11. Tanner, F. H., and McDonald, J. R.: Arch. Path. **36**:358, 1943.

THE REACTION TO BIREFRINGENT PARTICULATE MATTER

Granulomas produced by bacteria or viruses should not be confused with granulomas produced by particulate matter. Microscopy carried out with polarized light aids in distinguishing between the two. The possibility also must be considered that the original lesion was caused by a micro-organism but that the persistence and the type of lesion are results of the presence of some crystalline material added later. The causative agent may be an abnormal metabolic product, a secretion outside its normal duct system, or a foreign body introduced from the outside. Studies of breast, gallbladder, prostate gland, thyroid gland and ileum carried out under polarized light reveal that a granulomatous lesion can result from the presence of crystals or paracrystals. The size and the nature of the particles determine the lesion. If talc is taken as an example, it will be found that particles less than 0.5 micron in size produce an epithelioid response and that larger particles produce a granuloma, whereas particles more than 10 to 12 microns in size are engulfed in foreign body giant cells without surrounding reaction. Cholesterol esters, finely ground asbestos, and sericite may produce lesions similar to the lesion produced by talc. In experiments embodying subcutaneous injection, much depends on what animal is being used, because tubercles do not develop readily in dogs. Finely divided cellophane and silica will produce progressive fibrosis. Wheat dust will produce a localized fibrous nodule. Fibrous asbestos produces progressive fibrosis in the lung, but if it is ground up and injected, its action resembles that of talc.

Cholesterol esters demonstrate the effect of the molecular arrangement on the response of the tissues. In the paracrystalline state cholesterol esters are tolerated as an innocuous inclusion. So-called liquid crystals exist in cells without the production of a reaction. But when the molecular organization changes, and there is an increase in the orientation of the molecules so that a rosette of acicular crystals forms, the mass becomes a foreign body. The crystals produce a lesion resembling that produced by talc, with the production of pseudotubercules.

The physicochemical aspects of cholesterol metabolism are still obscure. Cholesterol metabolism is important because of its relationship to the development of atheromatous plaques in large vessels. In youth, deposited lipids can be reabsorbed. That is, the lipid does not attain to a physical state that will not permit reabsorption. As the age of the person advances, the lipid proceeds beyond the point at which reversal equilibrium can be obtained, just as cholesterol esters, in changing from the paracrystalline phase, become foreign bodies.

It is possible to find cholesterol esters in the presence of any long-standing infection. Although they are products of the infection, they themselves exert an irritant action. For instance, in a study of

granulomatous lesions of the terminal portion of the ileum, a mass of crystals was seen being extruded into the lumen of the intestine (fig. 4).

To assist in distinguishing between free and combined cholesterol in sections, it has been suggested that the sections be treated with digitonin and examined under a polarizing microscope. In our experience, the birefringence of cholesterol digitonin has prevented such distinction. Furthermore, the worker cannot depend on solution in lipid solvents to extract these substances. Although the cholesterol esters of short chain or unsaturated fatty acids are freely soluble in alcohol, the solubility of the palmitic and stearic esters at room temperature is about 0.03 Gm. per hundred cubic centimeters. For this reason,

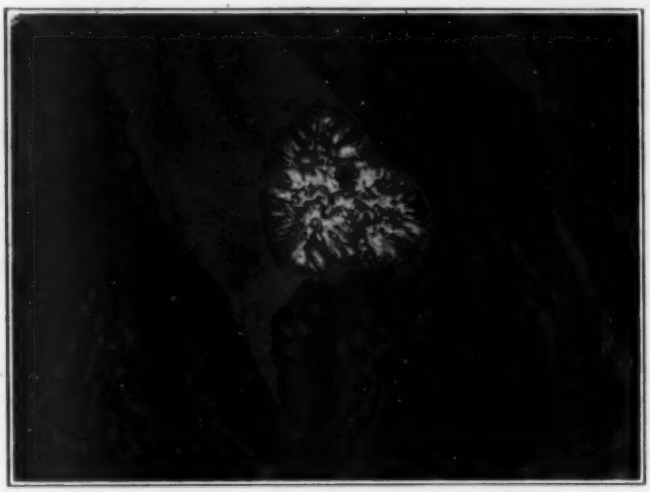

Fig. 4.—Section depicting a possible mode of excretion of cholesterol esters. This is a section of the terminal portion of the ileum of a patient who had an inflammatory granuloma of the ileocecal region. The cholesterol ester mass is being extruded through the mucous membrane. The mucosa and the submucosa contained many particles of cholesterol esters, with a few which had a foreign body reaction around them (× 200; polarizers at half extinction).

and because formaldehyde-precipitated proteins protect the crystals, the worker may see the crystals in routine paraffin sections that have spent hours in lipid solvents.

SUMMARY

Benefits are to be gained by the use of the polarizing microscope in pathology. Polarized light permits visualization of lipid aggregates, crystals and subcellular structures not visible in ordinary light. The anisotropism, or the orientation that produces birefringence in tissues that support, move or protect organisms or conduct nervous impulses, is fundamental in the organization and function of such tissues. In the development of tissues the anisotropic substances or oriented molecules tend to induce mutual adlineation in similar substances adjacent to them.

EXPERIMENTAL ATHEROSCLEROSIS

IX. The Effect of Prolonged Feeding of Egg Yolk Powder in Rats

J. A. ROSENKRANTZ, M.D.
AND
MAURICE BRUGER, M.D.
NEW YORK

ATHEROSCLEROSIS may be produced readily in rabbits by the feeding of cholesterol. The literature on this subject has been reviewed by Duff.[1] In guinea pigs, too, atherosclerosis may be similarly produced, but with more difficulty.[2] Attempts to obtain these vascular changes in rats, mice, cats, dogs, monkeys, goats, foxes, chickens, pigeons and parrots have been unsuccessful.[1]

Hypercholesteremia and atherosclerosis readily develop in the rabbit because this animal is unable to metabolize exogenous cholesterol.

Atherosclerosis may develop in human beings even in the presence of only a moderate increase of blood cholesterol, but it is felt that the lesion produced in the rabbit is not identical with that of human arteriosclerosis. Numerous studies agree with this point of view.[3] On the other hand, Leary[4] suggested that hypercholesteremia hastens the formation of arteriosclerotic plaques in human beings and that the experimental vascular lesion seen in the aorta of the cholesterol-fed rabbit is the counterpart of the lesion found in human tissues.

Some investigators have attempted to produce hypercholesteremia in human subjects by diets rich or poor in fat or by diabetic diets but have either failed or have been only partially successful after long periods.[5] Corwin[6] was able to increase blood cholesterol in dogs by

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From the Medical Research Laboratory, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Duff, G. L.: Arch. Path. **20**:81, 1935.

2. Bailey, C. H.: Proc. Soc. Exper. Biol. & Med. **13**:60, 1915.

3. Page, I. H.; Kirk, E., and Van Slyke, D. D.: J. Clin. Investigation **15**: 109, 1936. Landé, K. E., and Sperry, W. M.: Arch. Path. **22**:301, 1936. Page, I. H.: Ann. Int. Med. **14**:1741, 1941. Elliot, A. H., and Nuzum, F. R.: Arch. Int. Med. **57**:63, 1936. Hunt, H. M.: New England J. Med. **201**:659, 1929.

4. Leary, T.: Arch. Path. **21**:459, 1936; J. A. M. A. **105**:475, 1935.

5. Gardner, J. A., and Gainsborough, H.: Biochem. J. **22**:1048, 1928. Steiner, A., and Turner, K. B.: J. Clin. Investigation **19**:373, 1940. Bruger, M., and Somach, I.: J. Biol. Chem. **97**:23, 1932.

6. Corwin, W. C.: Arch. Path. **26**:456, 1938.

feeding them lecithin for six weeks. Steiner and Domanski [7] confirmed these findings in dogs and human subjects, using egg yolk powder as the source of lecithin. Sperry, Jailer and Stoyanoff [8] also demonstrated that the serum cholesterol level may be elevated in monkeys after three days' feeding of egg yolk. Steiner and Domanski [7] showed that feeding of egg yolk powder to patients in addition to a high caloric diet for six to ten weeks resulted in a rise in serum cholesterol and in body weight.[9] A similar diet increased the serum cholesterol in dogs without the production of atherosclerosis or fatty infiltration of the liver and other organs.[7] In monkeys the feeding of two to five eggs or egg yolks failed to alter the blood cholesterol level during the following twenty-four hours. On the other hand, an increase was noted in the free cholesterol fraction and especially in the cholesterol esters when the egg feeding was continued for an additional three days.[8]

Since diets enriched with egg yolk have been shown to produce hypercholesteremia in man, monkeys and dogs without vascular sclerosis, this investigation was extended to include white rats.

MATERIAL AND METHOD

Ten male white rats weighing 240 to 278 Gm. were employed in this study. Six rats were fed ad libitum a paste mixture [10] of egg yolk powder and ground Purina dog chow checkers in the ratio of 1:4 for three months and then a paste of pure egg powder [11] alone for the next six months. The remaining 4 rats served as controls and were fed only Purina dog chow checkers.[12] In both groups drinking of water was freely permitted. The animals seemed in perfect health throughout the experimental period, ate well and gained weight regularly.

At monthly intervals the systolic blood pressure of each animal was determined by the method of Williams, Harrison and Grollman.[13] At regular intervals the animals were weighed, and blood was withdrawn by cardiac puncture for the determination of blood cholesterol. Cardiac aspiration caused the death of 3 experimental animals at three, six and eight months, respectively. Whole blood

7. Steiner, A., and Domanski, B.: Am. J. M. Sc. **201**:820, 1941.

8. Sperry, W. M.; Jailer, J. W., and Stoyanoff, V. A.: Federation Proc. **1**:135, 1942.

9. Steiner, A.: J. A. M. A. **116**:2752, 1941.

10. Analysis (by Elsie V. Frost, B. A., New York Post-Graduate Hospital) showed total lipid 33 per cent, fatty acids 31.8 per cent, total cholesterol 1.2 per cent, cholesterol esters 0.8 per cent, lipid phosphorus 0.3 per cent and lecithin 7.8 per cent.

11. Analysis (by R. C. Williams & Co., New York) showed lecithin 14.4 per cent, vitellin 31.6 per cent, nuclein 3 per cent, cerebrin 0.6 per cent, glycerophosphoric acid 2.4 per cent, cholesterol 8 per cent, fats 40.6 per cent, coloring matter 1 per cent, salts 2 per cent and water 3.6 per cent.

12. Analysis (by Ralston Purina Co., St. Louis) showed protein 22.5 per cent, fat 5.5 per cent and carbohydrates (nitrogen-free extract) 50.25 per cent.

13. Williams, J. R., Jr.; Harrison, T. R., and Grollman, A.: J. Clin. Investigation **18**:373, 1939.

was analyzed for cholesterol by Sackett's modification of Bloor's method.[14] At the end of nine months, the remaining 3 experimental and 4 control animals were killed by a blow on the head, and sections of the aortas, livers, kidneys, spleens and lungs were taken for gross and microscopic study. Microscopic sections of tissues fixed in Bouin's solution were stained with hematoxylin-eosin. For qualitative estimation of fat content, tissues were fixed in solution of formaldehyde U. S. P. and stained with sudan III.

In addition, the livers were analyzed[15] for total cholesterol and lipid phosphorus; the latter was determined by the Whitehorn method.[16] For these analyses, the livers were cut into small slices, and 20 cc. of 25 per cent potassium hydroxide was added for each gram of wet liver. Hydrolysis was carried out on an electric hot plate for three hours, and then the material was cooled. Extraction was done in a separatory funnel, four successive 100 cc. samples of ether being used. Each of the four ether fractions was washed with the same 10 cc. portion of water. All of the ether samples were combined and evaporated to dryness. Whenever the residue was colored, it was reextracted with purified benzin U. S. P. and again evaporated to dryness. The residue was taken up in 20 cc. of chloroform, and 1 cc. of the preparation was used for analysis.

RESULTS

The chart illustrates the changes observed in whole blood cholesterol, systolic blood pressure and body weight during the prolonged feeding of egg yolk powder to 6 white male rats, which were compared with 4 control white male rats fed a normal diet. In the experimental group the whole blood cholesterol was elevated throughout most of the observation periods, the greatest increase occurring in the last four months.

The blood pressure was only slightly elevated in each group during the early months of the study and showed a gradual but definite decline toward the end of the experimental period.

Both the experimental and the control animals gained weight at approximately the same rate throughout the study. In the last few months the average gain of the rats fed egg yolk was slightly greater than that of the control rats. However, during the first three months, when the experimental animals received the mixed diet (egg: dog chow checker-1: 4) the rate of change of the whole blood cholesterol and of the body weight was less notable.

Necropsies resulted in the following observations: After three months of experimentation 1 rat revealed neither gross change in any of its organs nor microscopic evidence of increased deposition of fat in the liver. However, 2 rats examined grossly after six and eight months, respectively, showed slight to moderate increase of fat in the perirenal tissues, in the subcutaneous tissues and in the liver; no other changes were demonstrable in any of the other organs, including the aorta. Microscopically, too, there was an increase in hepatic fat deposits. At the completion of nine months all the rats fed egg yolk revealed markedly increased storage of fat in the subcutaneous depots, the mesentery, the perirenal areas and the liver; none was evident in the other organs, including the aorta. Special study of the latter failed to show any atherosclerotic plaques. Microscopically, these findings were confirmed and large amounts of fat were found deposited in the

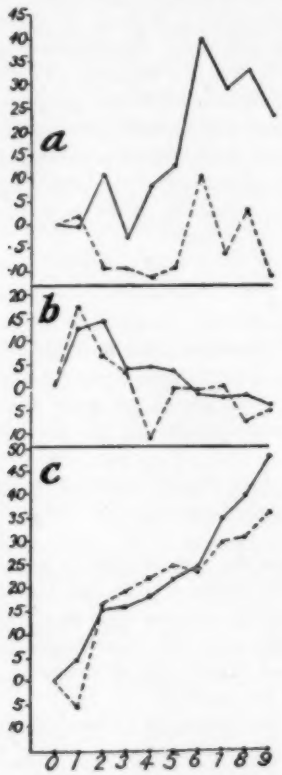
14. Sackett, G. E.: J. Biol. Chem. **64**:203, 1925.

15. With the technical assistance of Samuel Member, B.S., New York Post-Graduate Hospital.

16. Whitehorn, J. C.: J. Biol. Chem. **62**:133, 1924-25.

portal areas of each hepatic lobule while none was evident in the aorta. In the rats fed a normal diet no gross or microscopic changes were demonstrated.

In 4 control and 3 experimental rats the cholesterol and lipid phosphorus contents of the wet liver were determined. The cholesterol content of the liver averaged 260 mg. per hundred grams in the control animals and 672 mg. per hundred grams in the experimental rats. The lipid phosphorus content of the liver calculated as lecithin[17] averaged 17 mg. per hundred grams in the control and 14 mg. per hundred grams in the experimental animals.



Average percental change in (*a*) whole blood cholesterol, (*b*) systolic blood pressure and (*c*) body weight in 6 white rats fed egg yolk powder (solid line) and 4 controls fed a normal diet (broken line). The numbers at the left represent percentages; those at the bottom, months.

COMMENT

In the present study, in which rats were fed egg yolk powder for prolonged periods, blood cholesterol was increased over the initial level without the development of atherosclerosis. It is possible that lecithin, which has been shown to produce hypercholesteremia,[6] inhibits the

17. Mattice, M. R.: Chemical Procedures for Clinical Laboratories, Philadelphia, Lea & Febiger, 1936, p. 94.

deposition of cholesterol in the aorta because of its choline content. This point of view has been maintained by Steiner,[18] who suggested that choline causes reabsorption of atheromatous lesions produced in the aortas of cholesterol-fed rabbits. Steiner [19] and Kesten and Silbowitz [20] observed that choline delayed the production of, or partly prevented, atherosclerosis in rabbits. In addition, Meeker and Kesten [21] were able to diminish the incidence and the degree of atherosclerosis in cholesterol-fed rabbits by feeding a high protein diet of soybean flour. On the other hand, Baumann and Rusch [22] and Himsworth [23] found that choline did not prevent deposition of cholesterol in the aortas of rabbits fed cholesterol.

So far as deposition of fat in the liver is concerned, this investigation demonstrated a marked increase of fat in the portal areas of each lobule and a quantitative increase of cholesterol in the liver. This confirms the findings of earlier studies.[24] On the other hand, it has been shown that lecithin and choline [25] have definite lipotropic properties and that yeast or other rich sources of the vitamin B complex added in large amounts to the diet protected against or produced clinical improvement in cirrhosis.[26] Other investigators have pointed out that lack of certain food factors such as those found in yeast caused impairment of function as well as fatty and cirrhotic changes in the liver.[27] Furthermore,

18. Steiner, A.: Proc. Soc. Exper. Biol. & Med. **39**:411, 1938.

19. Steiner,[18] p. 231.

20. Kesten, H. D., and Silbowitz, R.: Proc. Soc. Exper. Biol. & Med. **49**:71, 1942.

21. Meeker, D. R., and Kesten, H. D.: Arch. Path. **31**:147, 1941; Proc. Soc. Exper. Biol. & Med. **45**:543, 1940.

22. Baumann, C. A., and Rusch, H. P.: Proc. Soc. Exper. Biol. & Med. **38**: 647, 1938.

23. Himsworth, H. P.: Acta med. Scandinav. (supp.) **90**:158, 1938.

24. Chalatow, S. S.: Virchows Arch. f. path. Anat. **207**:452, 1912. Anitschkow, N., and Chalatow, S. S.: Centralbl. f. allg. Path. u. path. Anat. **24**:1, 1913. Bailey, C. H.: J. Exper. Med. **23**:69, 1916. McMeans, J. W.: J. M. Research **33**:475 and 481, 1916. Kimura, T.: Tr. Jap. Path. Soc. **21**:370, 1931. Okey, R.: J. Biol. Chem. **100**:lxxv, 1933.

25. Best, C. H.; Hershey, J. M., and Huntsman, M. E.: J. Physiol. **75**:56, 1932. Best, C. H., and Huntsman, M. E.: ibid. **75**:405, 1932. Best, C. H.; Mawson, M. E. H.; McHenry, E. W., and Ridout, J. H.: ibid. **86**:315, 1936. Kesten and Silbowitz.[20] Himsworth.[23]

26. Von Glahn, W. C., and Flinn, F. B.: Am. J. Path. **15**:771, 1939. Kensler, C. J.; Sugiura, K.; Young, N. F.; Halter, C. R., and Rhoads, C. P.: Science **93**:308, 1941. Patek, A. J., Jr., and Post, J.: J. Clin. Investigation **20**:481, 1941.

27. Lillie, R. D., and Sebrell, W. H., in The Pathology of "Yellow Liver" of Dogs, National Institute of Health Bulletin no. 162; Treasury Department, Public Health Service, 1933, p. 23. Rhoads, C. P., and Miller, D. K.: J. Exper. Med. **67**:463, 1938. György, P., and Goldblatt, H.: ibid. **70**:185, 1939. Rich, A. R., and Hamilton, J. D.: Bull. Johns Hopkins Hosp. **66**:185, 1940.

Blatherwick and his co-workers [28] showed that the fatty liver observed on feeding rats raw liver, dried whole liver or cooked whole eggs resisted the lipotropic action of lecithin.

To further complicate the picture, Himsworth and Glynn [29] described two pathologic states of the liver which were produced by dietary means: first, massive hepatic necrosis like acute yellow atrophy due to the lack of a protein component and prevented [30] by the addition of casein or methionine but not by that of cystine or choline and, second, diffuse hepatic fibrosis like portal cirrhosis resulting from long-continued fat infiltration of the liver and inhibited by [29] the administration of yeast and choline. These workers further pointed out that most previous studies of hepatic damage caused by dietary insufficiency and of the effects of lipotropic substances thereon were confusing because of the failure to recognize two distinct pathologic states.

It is possible that fat was deposited in the livers of the rats used in this study because the diet, which consisted wholly of egg yolk powder, was inadequate in the substances found in yeast or other sources of the vitamin B complex. The lecithin in egg yolk powder, despite its choline content, was probably insufficient in amount, or its lipotropic activity was antagonized by the large amounts of cholesterol and proteins found in egg.

Steiner [31] demonstrated a weight gain in patients with chronic disorders when egg yolk powder was added to the diet; high caloric diets alone failed to give an increase of weight in these patients. His observation is not entirely confirmed in this study on rats, since the feeding of egg yolk powder failed to accentuate weight gain appreciably. Necropsies of the rats fed egg yolk powder revealed a marked increase of fats in all the depots and this should have caused a much greater increase of body weight. It is conceivable that this discrepancy may have been due to fat replacement of muscle fibers.

The rats fed egg yolk powder did not disclose an increase in systolic blood pressure. This may be ascribed to the fact that no observable vascular damage occurred in experimental rats. A slight decrease in blood pressure was noted in both control and experimental rats toward the end of the investigation. This may have been due to the adjustment of the rats to handling and environment, or perhaps to myocardial damage produced by the cardiac punctures made at monthly intervals.

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28. Blatherwick, N. R.; Medlar, E. M.; Bradshaw, P. J.; Post, A. L., and Sawyer, S. D.: Proc. Soc. Exper. Biol. & Med. **29**:345, 1931; J. Biol. Chem. **97**:xxxiii, 1932; **100**:xviii, 1933; **103**:93, 1933.

29. Himsworth, H. P., and Glynn, L. E.: Clin. Sc. **5**:93, 1944.

30. Himsworth, H. P., and Glynn, L. E.: Clin. Sc. **5**:133, 1944.

31. Steiner and Domanski.[7] Steiner.[9]

SUMMARY

The prolonged feeding of egg yolk powder to rats augmented the cholesterol content of the blood and the liver but failed to produce atherosclerosis of the aorta. The lecithin content of the liver was not increased by feeding of egg yolk.

Deposits of fat appeared in the liver six to nine months after the feeding of egg yolk was begun. It follows that under the conditions of this experiment the lecithin present in egg yolk failed to inhibit lipoid infiltration of the liver.

During the latter months of the experiment the rats fed egg yolk powder gained weight more rapidly than did the control rats.

The systolic blood pressure was not elevated in rats fed egg yolk powder.

Case Reports

TUMOR OF THE THORACIC INLET PRODUCING THE PANCOAST SYNDROME

A Report of Seventeen Cases and a Review of the Literature

PETER A. HERBUT, M.D., and JOHN S. WATSON, M.D., PHILADELPHIA

IN 1838 Hare reported on an illness in a man 40 years of age that began with pain, tingling and numbness along the course of the left ulnar nerve, pain in the left shoulder and swelling of the left elbow, all of one month's duration. Examination disclosed a small tumor in the inferior triangular space of the left side of the neck, a constricted left pupil and a drooping left eyelid. Within three weeks the tumor became larger and the pain more severe. Gradually the lower extremities became numb, cold and then completely paralyzed. Death occurred two and one-half months after the onset of symptoms. Necropsy disclosed edema of the legs and the left arm and a large scirrhous mass in the left side of the neck. The tumor involved the carotid and subclavian arteries and the corresponding veins and the pneumogastric, phrenic and recurrent laryngeal nerves; it pressed on the brachial plexus; it was firmly attached to the spine at the origin of the third and fourth nerves of the plexus, both of which were inseparable from the tumor, and extended into the dura of the spinal cord along the course of the eighth cervical and first dorsal nerves. No carcinoma was demonstrable elsewhere.

In 1850 MacDonnell reported on a similar illness in a girl 17 years old. A tumor gradually developed in the left supraclavicular region, accompanied by pain in the left shoulder and arm, loss of power with atrophy of muscle and edema of the left arm, constriction of the left pupil and ptosis of the left eyelid, cough, dyspnea, partial paralysis, and incontinence of urine and feces. Superficial veins over the tumor became dilated, and pulsation of the left brachial, ulnar and radial arteries was completely obliterated. The patient died in dyspnea. At autopsy an encephaloid tumor of the left lung was found that had extended into the base of the neck, where it was indented by the clavicle and attached to the cervical vertebrae. The tumor surrounded the brachial plexus, pressed on the cervical sympathetic chain, stretched the left subclavian vein and obliterated the third portion of the corresponding artery. It had metastasized to the right lung. In 1918 Ricaldoni (quoted by Romano and Eyherabide) described a carcinoma of the lung occurring in a man 65 years of age, which had invaded the first dorsal vertebra and produced pain in the right shoulder and arm, loss of power and atrophy of muscle of the right arm and hand, and Horner's syndrome on the right side. There were metastases in the cervical lymph nodes. The duration of the illness was five months. In 1921 Freeman reported on a patient 53 years old who, because of pain in the left arm, was thought to have a tumor of the spinal cord.

From the Clinical Laboratories, Jefferson Medical College Hospital.

At operation a neoplasm was not found, but subsequent roentgenograms disclosed a tumor at the apex of the left lung that was diagnosed histologically as endothelioma of the pleura.

Apparently unaware of the first three of the aforementioned papers, Pancoast in 1924, under the title "Importance of Careful Roentgen Ray Investigations of Apical Chest Tumors," described 3 cases, and again in 1932, under the title "Superior Pulmonary Sulcus Tumors," added 4 others that were essentially similar to the cases already referred to. Although in none of his cases was an autopsy performed and although material was removed for histologic study in only 3 cases, Pancoast expressed the belief that he was dealing with a new entity—a specific tumor arising in an embryonal epithelial rest which was possibly derived from the fifth pharyngeal pouch. As prerequisites for a correct diagnosis of the syndrome he listed the following: location of the thoracic inlet in the region of the superior pulmonary sulcus, pain around the shoulder and down the arm, atrophy of the muscles of the hand, Horner's syndrome and, roentgenographically, a small homogeneous shadow at the extreme apex with more or less local destruction of ribs and infiltration of vertebrae. He expressed the belief that primary tumor of the lung, the pleura, the ribs or the mediastinum could be excluded by the absence of one or more of the foregoing characteristic manifestations. He was, however, careful to state that "it is possible that this new designation may be changed again with a better knowledge of the histopathology of the growth."

Time has borne out the truth of the last statement, for complete necropsies of patients with this syndrome have shown that it is the location of the tumor which is important in producing the chain of symptoms described, and not its histologic structure. It has further been shown that the latter is not uniform but varies from case to case. A search of the medical literature discloses records of 134 cases, including those referred to in the foregoing paragraphs. (A bibliography of the reported cases accompanies this article.)

While in most of these cases the growth has been described as originating in the lungs, almost all other organs have served as primary sites for tumors metastasizing to the thoracic inlet and producing the characteristic clinical manifestations. As will be seen subsequently, however, there are also cases in which a careful autopsy disclosed no primary site other than the soft tissues of the neck, thus confirming Pancoast's original impression that the tumor may arise in an embryonal rest.

It is the purpose of this paper (1) to record 17 cases of tumor of the thoracic inlet which we have encountered at the Jefferson Medical College Hospital in the last six years and which fulfil all or most of the criteria outlined by Pancoast and (2) to analyze the data on all similar cases hitherto recorded of which reports were available to us.

REPORT OF CASES

Primary Carcinoma of the Lung.

CASE 1.—A white man 39 years old was well until nine weeks before admission, when severe pain developed in the left shoulder, which occasionally radiated down the arm. Gradually there developed weakness, loss of weight, slight cough,

hoarseness, numbness of the legs and difficulty in walking. Examination disclosed shotty nodes in the neck, dulness at the apex of the left lung, Horner's syndrome on the left side, paralysis of the left vocal cord and xanthochromia of the spinal fluid with evidence of block. Bronchoscopy revealed no abnormality. Roentgenograms of the chest showed an infiltration of the upper lobe of the left lung and erosion of the transverse process of the second dorsal vertebra. Gradually paralysis became more severe, and the patient died three and one-half months after the onset of symptoms.

At necropsy there was a primary tumor in the main bronchus to the upper portion of the upper lobe of the left lung that measured 1.5 cm. in length. The bronchial lumen was constricted, and there were several bronchiectatic and abscess cavities distal to the tumor. From the mucosa the neoplasm extended through the bronchial wall and was continuous with a tumor mass 4 cm. in diameter that filled the concavity of the aortic arch and contained the left recurrent laryngeal nerve. Attached to this mass were several other tumors, one of which occupied the left thoracic inlet (fig. 1). This tumor measured 3.5 cm. in diameter; it completely surrounded the second portion of the subclavian artery and partially encircled and compressed the most inferior bundle of the brachial plexus. Medially it engulfed the inferior portion of the cervical sympathetic trunk, was adherent to the body of the first dorsal vertebra and almost completely replaced that of the second dorsal vertebra. From the latter it extended into the spinal canal, along which it spread for a distance of 4 cm. and compressed the corresponding portion of the spinal cord. There were metastases in each kidney and in the abdominal lymph nodes. Microscopically, both the primary tumor and the secondary growths disclosed the usual pleomorphism characteristic of bronchogenic carcinoma. The tumor cells were round or irregular, contained a moderate amount of cytoplasm and were arranged either diffusely or in adenomatous formation. The supporting stroma was dense, fibrous and abundant.

Case 2.—A white man aged 61 was admitted with a history of a lump on the left side of the neck, pain in the left shoulder and down the left arm, and numbness, tingling and coldness of the fingers of the left hand, all of eight weeks' duration. Within two months there developed swelling of the left hand, Horner's syndrome on the left side and pain in the right shoulder. Roentgenograms of the chest first showed only infiltration of the upper lobe of the left lung but later disclosed a tumor in the upper part of the mediastinum and destruction of the lower cervical vertebra. The patient died five months after the onset of symptoms.

Necropsy disclosed a primary tumor 7 mm. long in a 4 mm. bronchus to the upper lobe of the right lung. The draining nodes were infiltrated with tumor and these were continuous with a mass 6 by 4 cm. in the anterior part of the mediastinum. This in turn was continuous with a tumor in the left thoracic inlet that measured 8 cm. in diameter. The neoplasm partially encircled the left subclavian artery and completely surrounded the lower trunks of the brachial plexus and the left recurrent laryngeal nerve. It eroded the posterior portion of the left rib and the eighth cervical vertebra. The left subclavian vein was thrombosed. There were metastases in the lower lobe of the left lung and the liver. Microscopically both the primary tumor and the metastatic growths disclosed anaplastic carcinoma of the "oat cell" variety in which there was a scanty stroma of connective tissue.

Case 3.—A white man 65 years old began to have pain in the right side of the face, the shoulder and the arm three months before admission. At the time of entry there were weakness of the right arm, dyspnea, cough with hemoptysis, dysphagia, hoarseness, paralysis of the right vocal cord, constriction of the pupil

and a large mass over the right mandible. Roentgenograms disclosed destruction of the right side of the mandible and "old tuberculosis" at the apex of the right lung. The patient died four months after the onset of pain.

Necropsy disclosed a primary tumor of the right main bronchus that measured 2 cm. in length. It penetrated the bronchial wall and produced an extrabronchial mass of firm gray tissue 4 cm. in diameter. This was continuous with a series of smaller masses in the superior part of the mediastinum, which were attached to a

Fig. 1 (case 1).—Anterior view of the tumor in the left thoracic inlet, where it engulfed some of the structures and compressed others: (*a*) cervical sympathetic trunk; (*b*) tumor; (*c*) brachial plexus; (*d*) subclavian artery; (*e*) subclavian artery.

tumor in the right thoracic inlet that measured 8 cm. in diameter. This neoplasm encircled the subclavian and common carotid arteries, the vagus and recurrent laryngeal nerves, and the inferior portion of the cervical sympathetic trunk. The upper branches of the brachial plexus passed over the tumor, while the lower

two roots were partially surrounded by the neoplastic tissue. Most of the first rib was destroyed by the tumor, and there were metastases in each kidney. Microscopically, both the primary tumor and the secondary growths were predominantly of a squamous cell variety.

CASE 4.—A white man 60 years old gave a history of progressive dyspnea and loss of 40 pounds (18 Kg.) in weight in the last five months. More recently he had suffered from repeated colds and a cough. He had pain down both arms, weakness of the right arm, and Horner's syndrome on the right side. One day after admission flaccid paralysis of the right arm and leg developed. He died on the following day.

Necropsy disclosed a primary tumor of the left main bronchus that measured 2.5 cm. in length. It penetrated the bronchial wall and infiltrated the mediastinum with a firm, solid, pink to gray mass 5 cm. in diameter. This was continuous with another mass, 14 by 6 cm., in the upper part of the mediastinum and the right thoracic inlet. The latter occupied the concavity of the first rib and protruded into the neck for a distance of 5 cm. It surrounded the first portion of the subclavian artery, the vagus and recurrent laryngeal nerves and the cervical sympathetic plexus. The lower roots of the brachial plexus as they left the foramens were pressed on but were not encircled by the tumor. There were metastases in the liver and the abdominal nodes. Microscopically, the tumor was of an anaplastic "oat cell" variety with some attempt at adenomatous formation.

CASE 5.—A 45 year old white man was admitted with the following complaints: pain in the left scapula of two years' duration, which was diagnosed as neuritis; cough with hemoptysis, of three months' duration; loss of weight; weakness of the left arm of six weeks' duration. He had Horner's syndrome on the left side slight hoarseness, dulness at the apex of the left lung and a shadow in the same region roentgenographically. He died three days after admission.

Necropsy disclosed a primary tumor in the left main bronchus 6 cm. beyond its origin, which had infiltrated the adjoining lung, was adherent to the first rib and occupied the region of the superior pulmonary sulcus. There were metastases in the kidneys, the adrenal glands, the mesenteric lymph nodes, the liver and the brain. Microscopically, the tumor was of a squamous and anaplastic cell variety and contained an abundant fibrous tissue stroma.

CASE 6.—A white man 48 years old strained his back two and a half months before admission. This was followed by pain that gradually increased in intensity. Four weeks later there were tingling and numbness in the lower extremities, with inability to walk and incontinence of urine and feces. At the time of entry there were dyspnea, Horner's syndrome on the right side, tumor in the right side of the neck and flaccid paralysis of the lower extremities. Roentgenograms showed a normal spine and bronchogenic carcinoma of the upper lobe of the right lung. The patient died one week after admission.

Necropsy showed the main bronchus to the upper lobe of the right lung occluded by a primary tumor 2 cm. long. It infiltrated the lung for a distance of 2 cm. and was continuous with a firm, gray mediastinal tumor 7 cm. in diameter. The upper portion of this projected into the right thoracic inlet, where it partially encircled the right subclavian artery and the recurrent laryngeal nerve and was adjacent to the inferior portion of the brachial plexus. Tumor tissue replaced almost all the vertebrae and from these extended directly into the spinal canal in six places. There were metastases in the pancreas, the liver, the colon, the lymph nodes and the testes. Histologically, the tumor was of an anaplastic cell variety.

CASE 7.—A white man 46 years old was admitted with pain in the right shoulder of two months' duration. Roentgenograms of the chest showed a tumor of the upper lobe of the right lung. At thoracotomy an inoperable cancer was found, and biopsy revealed squamous and adenocarcinoma. In spite of roentgen therapy the patient lost weight and became dyspneic. When he returned nineteen months later, he had Horner's syndrome on the right side, severe edema of the right side of the face, the neck and the upper extremity, pain in the right shoulder and down the right arm, a tumor in the left supraclavicular fossa and, roentgenographically, a tumor of the upper lobe of the right lung with destruction of the ribs and vertebrae. He died twenty-one months after the onset of pain. There was no autopsy.

CASE 8.—A white man aged 56 was admitted with continuous pain of the left side of the chest and the shoulder of eighteen months' duration. Gradually the pain extended down the left arm, and there developed cough, hoarseness, paralysis of the left vocal cord, dyspnea, Horner's syndrome on the left side, dulness and, roentgenographically, increased density of the apex of the left lung, and loss of weight. Thoracotomy disclosed irremovable carcinoma of the left lung. Biopsy of the tumor revealed anaplastic epithelial cells embedded in a dense fibrous tissue stroma. The patient was discharged from the hospital and there was no further follow-up.

CASE 9.—A white man 45 years old had pain in the anterior portion of the chest that radiated to the back and down the left arm of three months' duration. It was diagnosed as neuritis and treated with thirteen "electric treatments." Gradually there developed cough, loss of weight, and drooping of the left eyelid. Examination disclosed Horner's syndrome on the left side, dulness at the apex of the left lung and, by roentgenogram, a neoplastic infiltration of the upper lobe of the left lung. At operation an irremovable carcinoma of the left lung was encountered. Biopsy of the tumor disclosed large sheets of epithelial cells supported by a scanty fibrous tissue stroma, interpreted as compatible with a primary carcinoma of the lung. The patient was returned to the family physician for roentgen therapy.

Primary Bronchial Rest Carcinoma.

CASE 10.—A white man 57 years old complained of neuritis of the arm for eight months and cough and hoarseness for three weeks. Examination disclosed some swelling in the right supraclavicular fossa, and roentgenographically there was haziness of the medial border of the right upper lung field. Gradually the pain extended to the right side of the neck and the face and down the arm and became unbearable. There were paralysis of the right vocal cord, Horner's syndrome on the right side, loss of weight, dyspnea, dysphagia necessitating gastrostomy, edema of the neck, the shoulder and the arm, an increase in size of the supraclavicular tumor and, roentgenographically, partial destruction of the first right rib. He died eighteen months after the onset of pain.

Necropsy disclosed Horner's syndrome on the right side, edema of the entire upper extremity and a tumor in the right supraclavicular fossa. The latter was dense and sclerotic, and measured about 15 cm. in greatest diameter. It filled the entire right thoracic inlet, partially destroyed the manubrium, the clavicle and the inner portion of the first rib and was adherent to, but did not infiltrate, the vertebral bodies. It completely surrounded the subclavian artery and vein, the carotid vessels, the sympathetic plexus, the vagus nerve and the entire brachial plexus (fig. 2). Medially it pushed the esophagus and the trachea to the left, partly infiltrated these and extended over the trachea to the left side. The thyroid

gland was carefully examined. The left lobe was untouched, but the inferior pole of the right lobe was enveloped by the tumor. Everywhere, however, it was separated from the neoplasm by edematous connective tissue, and its capsule was intact. The visceral pleura of the apex of the upper lobe of the right lung was adherent to the tumor, but the lung was not invaded. The subclavian vessels were completely thrombosed. No tumors could be found in any other organs of the body, including the prostate, the mouth and the nasopharynx.

Microscopically, all sections disclosed an abundance of very dense, acellular fibrous tissue stroma containing cancer cells in anaplastic, adenomatous and

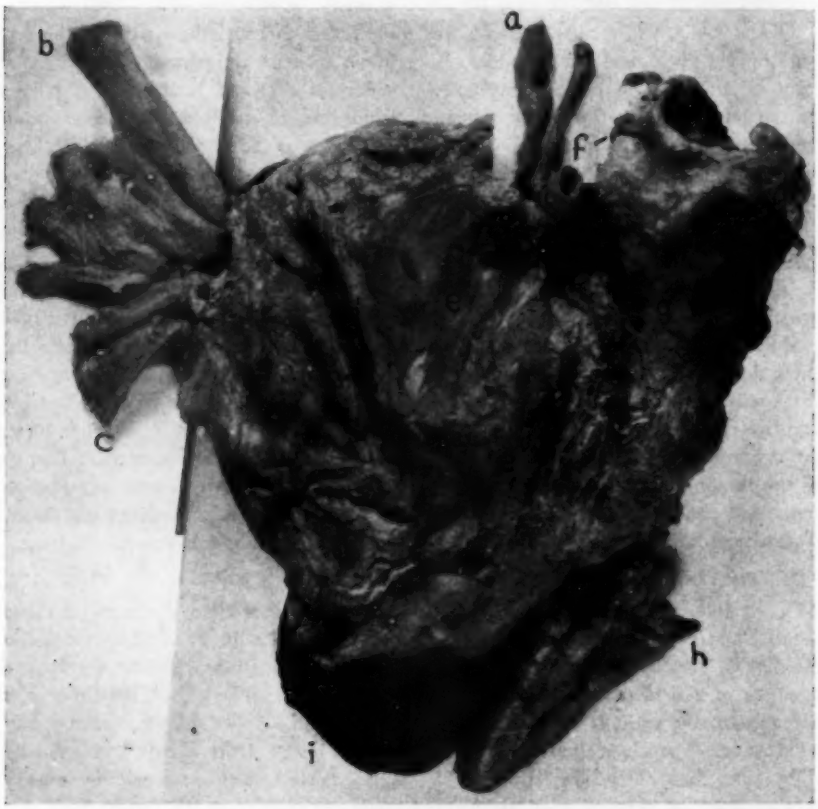

Fig. 2 (case 10).—Anterior view of a large scirrhous tumor of the right thoracic inlet, where it surrounded nerves and vessels. Note that the thyroid gland and the right lung are not a part of the tumor: (*a*) sympathetic plexus and vagus nerve; (*b*) brachial plexus; (*c*) axillary artery and vein; (*d*) clavicular groove; (*e*) tumor; (*f*) common carotid artery; (*g*) thyroid gland; (*h*) innominate artery; (*i*) lung.

squamous cell formation (fig. 3). The anaplastic cells were relatively small and round, oval or irregular, had abundant pink-staining cytoplasm and small, round or irregular, deeply stained nuclei. The cells in glandular formation were cuboidal, with abundant, less densely stained pink cytoplasm and round or oval vesicular nuclei in a basilar position. The cells arranged in squamous formation disclosed

indistinct borders, lightly stained pink cytoplasm and round or oval vesicular nuclei. Occasionally the masses contained hyaline bodies, but there were no definite pearls or intercellular bridges. Numerous sections were taken through the junction of the right lobe of the thyroid gland and the tumor, and in all the sections the latter was sharply demarcated from the former. Many sections from each lobe of the

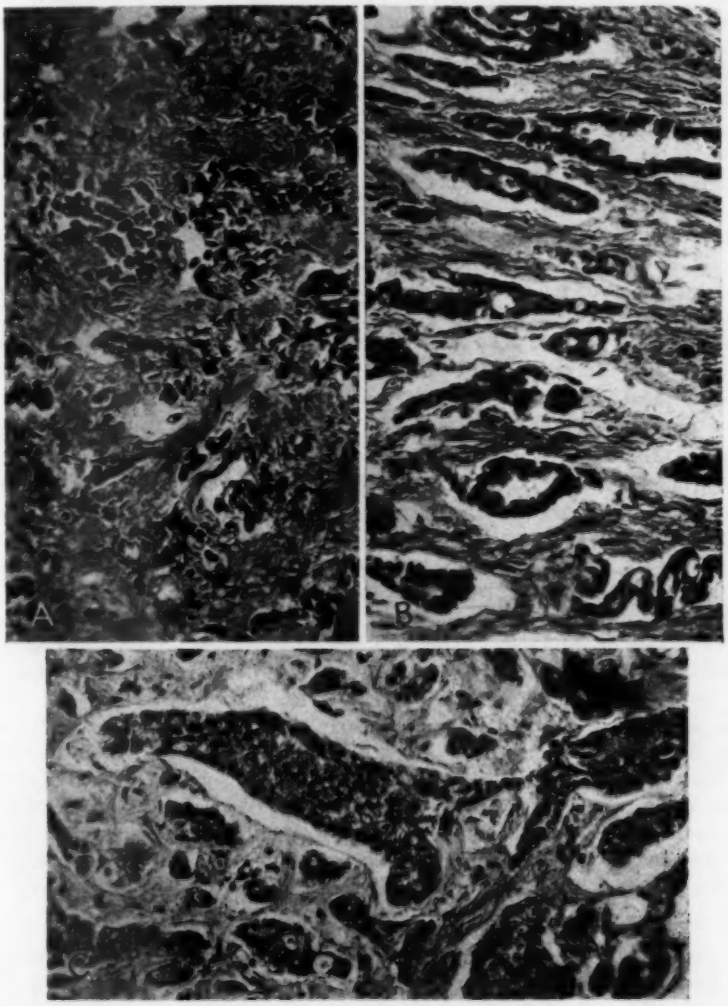

Fig. 3 (case 10).—*A*, section from the tumor mass showing a background of dense fibrous tissue containing anaplastic cancer cells. *B*, section from another portion of the tumor showing cancer cells in glandular formation. *C*, section from still another portion of the tumor showing the cancer in squamous cell formation. Hematoxylin and eosin. × 200.

thyroid gland likewise disclosed no cancer cells. They were, however, found within blood vessels in the tumor proper, in the medulla of one adrenal gland and in the interstitial tissue of one testis.

CASE 11.—A white man 52 years of age began to have pain in the left scapula and shoulder nine months before admission, which was diagnosed as neuritis. Gradually it became more severe and radiated down the inner aspect of the left arm. There developed a dry cough, dyspnea, paralysis of the left arm and both lower extremities and incontinence of urine and feces. Examination disclosed a mass in the left supraclavicular fossa, Horner's syndrome on the left side, edema of the left arm and hand and, roentgenographically, a mass in the neck encroaching on the apex of the left lung and partly destroying the first rib. He died one day after admission.

Necropsy disclosed a neoplasm in the left thoracic inlet that measured 8 cm. in diameter. It was very firm, gray to white, surrounded all the vessels and nerves in this region, was attached to the visceral pleura of the apex of the upper lobe of the left lung but did not penetrate the lung tissue, eroded the posterior portions of the first two ribs and the bodies of the corresponding vertebrae, and penetrated directly into the spinal canal, where it compressed the cord for a distance of 4 cm. Careful examination of all organs, including the thyroid gland and the prostate, disclosed no other tumors. Histologically the cancer was identical with that of case 10. There was a dense fibrous tissue stroma in which the neoplastic cells were in anaplastic, adenomatous and squamous cell formation. Only the pleura at the apex of the upper lobe of the left lung was involved with tumor. Sections of the thyroid gland and of the prostate disclosed no primary or secondary carcinoma, and there were no metastases to any of the other organs.

CASE 12.—A 39 year old white man gave a history of pain in the back and the right shoulder, dyspnea, cough and loss of weight, all over a period of eight months. Examination disclosed loss of power of the right arm, absence of Horner's syndrome and, roentgenographically, a mass in the apex of the right lung with destruction of the second and third ribs and of the bodies of the corresponding vertebrae. He died nine months after the onset of pain.

Necropsy disclosed a tumor occupying the right thoracic inlet and the base of the right side of the neck, measuring 8 cm. in diameter. It was firm, gray, and protruded into the thoracic cavity for 2 cm. It eroded portions of the first three ribs and the bodies of the corresponding vertebrae and compressed the adjacent spinal cord. The apex of the lung was infiltrated with tumor for a distance of 1 cm., and there were metastases in the kidneys. Histologically, as in cases 10 and 11, there was a background of dense fibrous tissue in which epithelial cells were embedded in anaplastic, adenomatous and squamous cell formation. In this case, however, the third type containing definite pearls predominated and the stroma was less abundant. There were metastases in the kidneys and in a cervical lymph node but not in any of the other organs.

Primary Carcinoma of the Thyroid Gland.

CASE 13.—A white woman aged 69 gave a history of nervousness, dysphagia and loss of weight of seven months' duration, and pain in the left side of the neck and down the left arm, with weakness of the left arm, of four months' duration. There were hoarseness, Horner's syndrome on the left side, a greatly enlarged, hard, tender thyroid gland and atrophy of the muscles of the left arm, followed by edema. A roentgenogram showed a tumor mass in the lower part of the neck, the mediastinum and the left thoracic inlet. The patient died eight months after the onset of symptoms.

Necropsy disclosed a scirrhous gray tumor replacing the entire left lobe of the thyroid gland and the lower three quarters of the right lobe and measuring 15 by 12 by 6 cm. (fig. 4). Inferiorly it extended beneath the sternum into the

anterior mediastinum, where it compressed the trachea to a narrow slit. Laterally it completely encircled the left subclavian and carotid vessels, the lower portion of the cervical sympathetic trunk, the left recurrent laryngeal nerve and the lower roots of the brachial plexus. The tumor did not destroy the ribs or the vertebrae, nor did it enter the spinal canal. There were metastases in the lungs, the heart, the left adrenal gland, the liver, the kidneys, the mucosa of the small bowel, the abdominal lymph nodes and the subcutaneous tissue of the back.

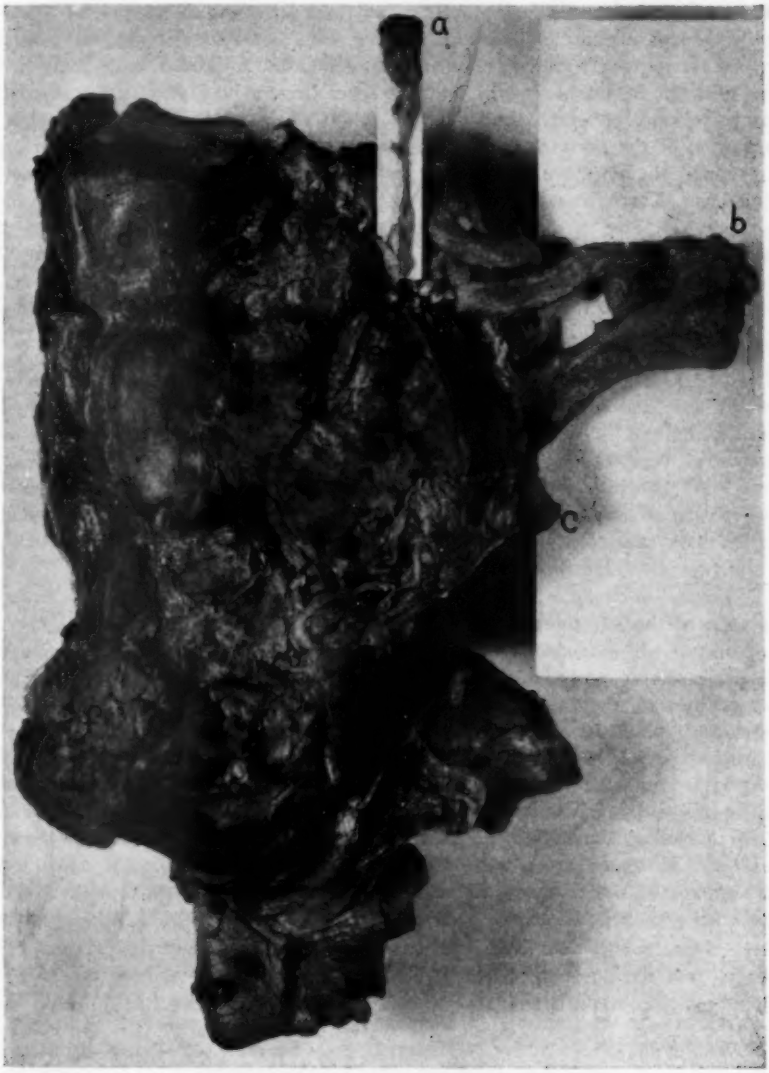

Fig. 4 (case 13).—Anterior view of a primary carcinoma of the thyroid gland engulfing all the vessels and nerves in the vicinity: (*a*) sympathetic nerve; (*b*) brachial plexus; (*c*) subclavian artery; (*d*) thyroid cartilage; (*e*) vagus nerve and common carotid artery; (*f*) tumor.

Histologically, most of the primary and secondary tumors were composed of round or spindle cells with a moderate amount of cytoplasm and round or oval, evenly stained nuclei arranged in a sarcomatous manner. There were other areas, however, that consisted of cuboidal cells in adenomatous and papillary formation, and still others composed of huge bizarre cells with abundant irregular cytoplasm and possessing equally huge and bizarre hyperchromatic nuclei.

CASE 14.—A Negro aged 58 stated that he noticed a change in his voice eight weeks previously. Soon there developed pain and swelling in the neck. Examination disclosed a large mass in the right anterolateral portion of the neck that measured 10 cm. in diameter. There were hoarseness, laryngeal paralysis, dyspnea, cough and dysphagia, and a roentgenogram showed a large mass in the neck pushing the trachea to the left. Dyspnea became so severe that tracheotomy was performed, at which time the tumor was observed to cover the trachea in the region of the thyroid gland, necessitating removal of a portion of it in order to produce an airway. The patient died about three months after the onset of symptoms. There was no autopsy, but histologic sections of tissue removed at operation disclosed a cancer very similar to that in case 13. Most of it was composed of round or spindle cells, producing a sarcomatous appearance, but there were also some polyhedral cells in an anaplastic distribution and others in an adenomatous formation.

Primary Mesothelioma of the Pleura.

CASE 15.—A white man 41 years old complained of pain and numbness of his left arm and loss of 45 pounds (20.5 Kg.) over a period of eight months. He also noticed "floods" of heat over the left side of his face and neck with absence of perspiration. Horner's syndrome was present on the left side, and there were dyspnea, dysphagia, cough, atrophy of muscle and loss of power in the left arm, fulness in the left supraclavicular fossa, dulness over the apex of the left lung and, roentgenologically, a tumor in the same region with destruction of the first rib. He died nine months after the onset of pain.

Necropsy disclosed a hard, gray, flat pleural and subpleural tumor covering the apex of the left thoracic cage. It measured 2.5 cm. in thickness and 14 cm. in diameter. It extended to the left and upper portion of the mediastinum and the pericardium, partly surrounded the subclavian artery, completely engulfed that portion of the brachial plexus posterior to this vessel together with the lower portion of the sympathetic plexus, and partly eroded the first two ribs. The upper part of the brachial plexus was not involved. The tumor extended to the pericardium, and there was a metastasis in the right crus of the diaphragm and in the adjoining lymph nodes, adrenal gland and kidney. The remaining organs, including the thyroid gland and the prostate, were normal. Histologically there was an abundant stroma of dense, acellular fibrous tissue in which there were groups of cancer cells. Some groups were solid and composed of irregular cells with abundant watery cytoplasm and irregular deep-staining nuclei, whereas others were in adenomatous formation wherein the cells, although similar, were cuboidal and the nuclei basilar in position. There were no tumors in either the thyroid gland or the prostate, or in any of the other organs not already referred to.

Primary Carcinoma of the Larynx.

CASE 16.—A white man aged 69 was admitted because of cough and pain in the right ear of several months' duration and hoarseness of three months' duration. Examination disclosed a firm right lobe of the thyroid gland and a primary cancer of the right vocal cord and the right side of the larynx. This was confirmed both

by biopsy and examination of the entire specimen after laryngectomy, when the growth proved to be a squamous cell carcinoma. Examination of the patient four months later revealed a fixed nodule above and to the right of the tracheal stoma and tenderness along the course of the great vessels. An attempt was made to extirpate the mass but, owing to the extensive involvement, all the tumor could not be removed. Histologic examination of removed tissue disclosed a squamous cell carcinoma. Nine months later the patient returned with severe pain in the right shoulder and down the right arm, and some dyspnea. Examination disclosed a large supraclavicular mass on the right side, "fixed to the brachial plexus," and Horner's syndrome of the right side. The patient was discharged from the hospital unrelieved of his pain and is still living.

Primary Hodgkin's Disease.

CASE 17.—A white man 21 years old was admitted with a history of a dry cough of two months' duration and swelling of the right side of the neck of three weeks' duration. There were enlarged lymph nodes in the right side of the neck and in the groins, and roentgen examination disclosed a mass in the superior mediastinum. Biopsy of one of the nodes revealed Hodgkin's disease, for which he was given roentgen therapy. He returned ten months later with dull pain in the left shoulder that radiated to the elbow. Horner's syndrome was noted on the left side, with dulness at the apex of the left lung, and roentgen examination showed a tumor in the superior mediastinum and the left thoracic inlet without apparent involvement of bone. He died fourteen months after the onset of symptoms.

Necropsy disclosed edema of the left side of the face and neck. In the upper and anterior mediastinum there was a gray firm nodular mass that measured 8 by 8 by 5 cm. It surrounded the main branches of the aorta and the left innominate vein and extended directly into the base and the left side of the neck and the left thoracic inlet, where it surrounded most of the structures. There was tumor involvement of the pleura, the diaphragm, the lymph nodes, the left sixth rib and the left kidney. Histologically the lesion was a typical one of Hodgkin's disease in which there was extensive fibrosis.

ANALYSIS OF REPORTED CASES

Nomenclature.—Although prior to 1924 there were isolated reports of tumor in the thoracic inlet producing the train of symptoms already referred to, it was not until Pancoast's report that such a syndrome became generally known. In his first paper Pancoast spoke of the lesion as "apical chest tumor" but in 1932 he changed the title to "superior pulmonary sulcus tumor" under the assumption that he was dealing with a specific tumor. While most subsequent authors used the latter title, the syndrome has been described under a variety of names. Some of the more commonly employed have been: "apico-costo-vertebral syndrome" (Tobias and other Latin American authors), "cancer of the thoracic pulmonary apex" (Pardal and Brea), "superior pulmonary sulcus syndrome" (Gilt and Trawbridge), "sulcus tumor" (Breslin), "primary apical lung carcinoma" (Steiner and Francis), "extrapulmonary tumors of the thorax" (Pierce), "sterno-clavicular branchiomas" (Fried), "tumor of the superior thoracic inlet" (Kelman and Schlezinger) and "Pancoast syndrome" (Fernandez and Fuste). Many other names, referring to specific tumors, have been used. Obviously, since any neoplasm, regardless of its origin, can produce

the signs and symptoms indicated, titles referring to a particular tumor or tumors should be avoided. Although in all our cases in which autopsy was performed, the subclavian artery was involved with tumor and therefore the neoplasm was in reality in the superior pulmonary sulcus, we believe that such a designation is too limited, for in each case the tumor also involved the entire thoracic inlet and even the base of the neck. We therefore believe that the neoplasms should be spoken of as tumor of the thoracic inlet. Also, since it was Pancoast who first emphasized the combination of tumor in the apex of the chest with more or less destruction of adjacent ribs and vertebrae, Horner's syndrome and pain down the arm, we believe that the simplest means of expressing this is by designating it as the Pancoast syndrome. For these reasons it is our opinion that the most suitable and comprehensive title is "Tumor of the Thoracic Inlet Producing the Pancoast Syndrome."

Clinical Considerations.—From the literature there were available to us reports on 134 cases, which together with the 17 cases included in this report make a total of 151 cases. In addition to these there are mentioned, particularly in discussions of papers read at meetings, 31 other cases. Since data on these are incomplete they will be omitted from discussion except when their inclusion is specifically mentioned.

Of the 151 patients, 137 were male and 14 female. The ages were 16 to 73 years, with an average of 48.6 years. The recorded duration of the illness from the initial symptoms to death in 113 cases averaged 10.5 months and ranged from two to thirty-two months. The right side was involved in 85 patients; the left side, in 66. A tumor mass was disclosed in the thoracic apex roentgenographically in 140 cases. The frequency of occurrence of the more important clinical manifestations was as follows: destruction of ribs, 72; destruction of vertebrae, 41; Horner's syndrome, 133; pain in the shoulder, 129, and down the arm, 122; loss of power in the arm, 99; dulness on percussion at the apex of the lung, 82; palpable supraclavicular tumor mass, 74, of which 58 were also visible; atrophy of the muscles of the arm, 71; cough, 48; dyspnea, 30; hoarseness, 22; edema of the arm, 20; laryngeal paralysis, 15, and hemoptysis, 6.

As is apparent from the accompanying photographs, all clinical manifestations in the syndrome can be accounted for on the basis of tumor involvement of the nerves and the blood vessels. The diagnosis is made from a consideration of the signs and symptoms, the roentgenograms of the apex of the chest and of the neck, and the results of biopsy of the tumor. When, however, the results of roentgen and histologic study are positive it is already too late. To date the disease has been 100 per cent fatal. Roentgen therapy so far appears to be of no avail, and certainly when the neoplasm is demonstrable by either physical or roentgen examination, one can be sure that the vital structures are involved to such an extent that complete surgical removal is impossible. Frequently, however, the patient has consulted a physician when pain in the shoulder and arm first developed, and because an obvious cause could not be found the condition has been diagnosed for months as neuritis. Obviously, if the tumor is metastatic, nothing in the way of curing it can be done even at an early stage, but if the lesion is primary in the neck, there may be a faint chance of complete extirpa-

tion when the tumor produces the first symptoms. It appears, therefore, that the cause of any persistent neuritis in the shoulder or the arm should be thoroughly investigated, even by surgical exploration if necessary.

Pathologic Considerations.—Autopsy was performed in 75 of the 151 cases, and biopsy alone in 29 others, making a total of 104 cases in which the tumor was studied histologically. There were 2 intraspinal lesions and 149 extraspinal neoplasms. The former consisted of syringomyelic cyst of the cord and leptomeningitis. The distribution of the primary cancers in the latter group were: carcinoma of the lung, 100; primary carcinoma of the neck, 21; endothelioma of the pleura, 5; carcinoma of the thyroid gland, 4; carcinoma of the breast, 3; carcinoma of the esophagus, 2; sympathoblastoma, 2; round cell sarcoma, hypernephroma, thymoma, mediastinal tumor, osteogenic sarcoma, carcinoma of the pancreas, neurogenic fibrosarcoma, chondrosarcoma, carcinoma of the stomach, carcinoma of the prostate, carcinoma of the larynx and Hodgkin's disease, 1 each. In the 32 cases mentioned but not described the distribution was: carcinoma of the lung, 10; sarcoma, 2; carcinoma of the breast, thymoma, carcinoma of the stomach, endothelioma of the pleura, sympathicoblastoma and Hodgkin's disease, 1 each. In the reports of 14 other cases the primary sites were not stated.

Of particular interest, perhaps, are those cases in which the tumor was said to have originated in the neck. In none of the cases without a complete and thorough autopsy can the tumor be designated as arising in the neck, and even if such an examination was made, one is hesitant in saying that some primary focus elsewhere was not missed. Thus, among the 18 cases in the literature that were thought to be instances of tumor of branchiogenic origin, there were only 5 (3 reported by Fried, Graf and Sternberg, and Clarke, respectively, and 2 by Morris and Harken) in which the tumor was examined completely enough to be accepted as possibly primary in the neck. Of these 5 cases, 4 were instances of squamous cell carcinoma and 1 was an instance of squamous cell and adenocarcinoma. To these may be added 3 of our cases (10, 11 and 12) in each of which the cells were in anaplastic, squamous and adenomatous formation.

If in these cases the tumor of the thoracic inlet was primary in the neck, then what structure was responsible for such a varied histologic picture? Most authors who have maintained that such a tumor may originate in the cervical region have expressed the belief that it arises from a branchiogenic rest (particularly the fifth), and Fried has even called it sternoclavicular branchioma. While this may be the explanation for those cases in which the tumor shows a pure squamous cell arrangement it can hardly account for those in which it shows in addition cells in anaplastic and adenomatous formations, because the branchial cyst is always lined with stratified squamous epithelium, and cancer developing from it is always of a squamous cell variety (Carp and Stout; Crile and Kearns). An origin from aberrant thyroid tissue cannot be easily dismissed except for the fact that although carcinoma of the thyroid gland is notoriously pleomorphic, squamous cells ordinarily are not one of the varied types of cells encountered. An explanation which has not been previously advanced and which to us seems most

plausible is that the tumor takes origin from a bronchogenic rest. The literature contains reports of 35 cases of bronchial cyst (Laipply). This probably arises as a pinching off of a portion of the foregut at the time of development of the trachea. It is located at some point along the course of the tracheobronchial tree and is lined with ciliated epithelium identical with that lining the trachea and the bronchi. Although no epithelium-lined cyst has been described in cases of primary carcinoma of the thoracic inlet, there is no reason why there may not be misplaced solid groups of cells arising in a similar manner from which such a neoplasm can arise. The location is correct for an origin from such a rest, and certainly the varied histologic picture presented in our 3 cases is highly reminiscent of ordinary bronchogenic carcinoma. This is to be expected since both the bronchial cyst and the bronchi and the trachea are lined with similar epithelium.

SUMMARY

A review of the literature discloses reports of 134 cases of tumor occurring in the thoracic inlet and producing the Pancoast syndrome. To these are added 17 cases, making a total of 151 cases. In the majority the tumor was secondary to a primary focus located in some organ of the body, with primary carcinoma of the lung predominating, although most organs have been named as the site of the primary growth. In 21 cases the tumor was thought to be primary in the neck but in only 8 of these was the examination thorough enough to exclude with reasonable certainty an origin in some distant organ. Because in some of these cases cancer cells were observed in squamous, anaplastic and adenomatous formations, it is believed that they may arise in bronchial rather than branchial rests.

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STEM CELL LYMPHOMA OF THE NEWBORN

MYRON S. ARRICK, M.D., NEW BRITAIN, CONN.

IN THE literature are many reports of various types of congenital cancer, but only a few contain unequivocal data revealing both the congenital and the cancerous nature of the disease. It is my purpose to discuss here the surprisingly high incidence of congenital cancers, and to report a case of congenital lymphoma of the stem cell type. To my knowledge there is no record of a similar case in the literature.

In view of Wells's [1] comprehensive critical analysis of the literature concerning congenital cancers, published in 1940, it would be superfluous to review the literature again at this time. Wells has classified all the reported cases as "accepted, probable or possible" cases, depending on the data given. He has summarized the material as shown in the accompanying table.

Summary of Recorded Congenitally Malignant Tumors (Not Including Retinal Tumors) (Quoted from Wells [1])

	Accepted	Probable	Possible	Total
Malignant renal tumors	5	11	?	16
Malignant adrenal neuroblastoma	17	15	21	53
Malignant extra-adrenal neuroblastoma	6	4	?	10
Congenital sarcoma	33	29	53	115
Teratoma, malignant at birth	1	2	?	3
Tumors of undetermined nature	3	1	7	11
Carcinoma of liver	0	1	9	10
Malignant hemangioendothelioma of liver	?	?	15	15
Hepatic tumors of undetermined character	?	?	4	4
Carcinoma, excluding liver	0	0	5	5
Cerebral glioma	1	1	2	4
Malignant endothelioma, excluding liver	?	?	5	5
Melanoma malignum	0	2	2	4
	66	66	123	255

It will be noted in the table that there is no accepted case of congenital carcinoma. Recently Ziegler [2] reported bilateral ovarian carcinoma occurring in a a 30 week old fetus. Congenital sarcoma, on the other hand, comprises the largest individual group of neoplasms, accounting for approximately half the total number of reports. It is to be remem-

From the Laboratory Division and Tumor Clinic, New Britain General Hospital, and the Department of Pathology, Yale University School of Medicine.

1. Wells, H. G.: Arch. Path. **30**:535, 1940.

2. Ziegler, E. E.: Arch. Path. **40**:279, 1945.

bered that the table deals with congenital cancers and that those listed differ from the types of cancer usually observed in infants, namely, (1) adenosarcoma, (2) retinoblastoma and (3) cancerous neurocytoma of the adrenal gland.[3] Whereas sarcoma occurred in approximately 50 per cent of the aforenamed highly selected cases,[1] no instance of a cancerous lymphoma is recorded. It is entirely likely, however, that cases of this type are submerged in the large group classified under the general heading "congenital sarcoma." Since Wells's comprehensive review in 1940, Rigby and Holinger [4] have reported the case of a 17 day old white boy with a mass in the larynx which proved on microscopic examination to be fibrosarcoma. The congenital nature of this tumor is open to question since it was first noted many days after birth.

A review of the literature under the general heading "congenital cancers" thus fails to establish an authentic instance of a congenitally cancerous lymphoma. Likewise, a survey of reports on cancerous lymphoma does not reveal any reported case of this disorder occurring at birth. Baldridge and Awie [5] reported 20 cases of lymphoma occurring in the first decade of life but gave no further analysis of the age incidence. The youngest patient in the 196 cases of lymphosarcoma reviewed by Sugarbaker and Craver [6] was a 4 year old child. The age incidence of the 545 cases of lymphoma reported by Gall and Mallory [7] is again given in decades, with 24 per cent of the cases of Hodgkin's disease, 18 per cent of the cases of lymphoblastic lymphoma and 11 per cent of the cases of lymphocytic lymphoma falling in the first two decades of life. The clasmatocytic lymphoma, the follicular lymphoma and, to a lesser degree, the stem cell lymphoma occurred predominantly in the older age group. In a personal communication Gall stated that in this series there was 1 case of congenital lymphoblastic lymphoma with leukemia. Jackson and Parker [8] expressed the opinion that it is uncommon for Hodgkin's disease to appear during infancy and extreme old age, but they admit that it may occur at any age. Smith [9] in 1934 added 23 cases of Hodgkin's disease of childhood to the 105 cases already noted in the literature. In 6 of the 105 cases the onset of the disease occurred during infancy—the infants ranging from 2 to 4 months of age. It is interesting to note that in 107 of the entire group of 128 cases the disease occurred in boys, being comparable in respect to the sex preference to leukemia and lymphoma. This superficial resemblance

3. Morehead, R. T.: Arch. Path. **38**:141, 1944.
4. Rigby, R. G., and Holinger, P. H.: Arch. Otolaryng. **37**:425, 1943.
5. Baldridge, C. W., and Awie, C. D.: Arch. Int. Med. **45**:161, 1930.
6. Sugarbaker, E. D., and Craver, L. F.: J. A. M. A. **115**:17 and 112, 1940.
7. Gall, E. A., and Mallory, T. B.: Am. J. Path. **18**:381, 1942.
8. Jackson, H., and Parker, F.: New England J. Med. **230**:1, 1944.
9. Smith, C. A.: J. Pediat. **4**:12, 1934.

is carried still further by Herbut, Miller and Erf,[10] who expressed the belief that Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma arise from a common parent call—the reticulum cell.

REPORT OF A CASE

A full term girl weighing 7 pounds, 8 ounces (3,402 Gm.) was born at New Britain General Hospital, Feb. 25, 1945, and at the time of birth had on the chest, over the manubrium, an irregular, smooth, salmon pink, waxy tumor. This measured 3 by 2 by 0.2 cm., being intimately associated with the skin and moving with the skin over the subcutaneous tissue. There was also a small palpable lymph node in the left axilla. The remainder of the immediate postnatal examination showed no abnormality.

The initial blood count was 4,800,000 erythrocytes; the hemoglobin content was 15.6 Gm.; the leukocyte count was 6,500, with neutrophils 65, eosinophils 3, lymphocytes 24 and monocytes 8 per cent. The patient's blood was type A and in addition her erythrocytes were Rh negative. The Rh types of the parents' erythrocytes are not known. Aside from a moderate reduction of the red cell count and of the hemoglobin content (controlled with multiple transfusions) repeated hemograms at a later date varied little from the foregoing picture. The initial urinalysis gave negative results. A biopsy of the subcutaneous tumor March 1 revealed leukemia cutis, and a biopsy of the enlarged gland of the left axilla March 7 revealed evidence of cancerous lymphoma. A roentgenogram of the chest March 8 showed nothing abnormal.

Roentgen therapy was started March 15, with good immediate results. The large tumor regressed but did not disappear. A few weeks later other cutaneous and subcutaneous masses appeared and were controlled by high voltage roentgen therapy. The patient was discharged to the tumor clinic April 19, weighing 8 pounds, 2 ounces (3,685 Gm.). While she was being followed in the tumor clinic, roentgen therapy was continued, but her general condition gradually and progressively declined. Numerous cutaneous and subcutaneous tumor masses appeared over many areas of the body.

The patient was readmitted to the New Britain General Hospital June 21, primarily because of difficulty in breathing. Examination revealed a dyspneic, malnourished and maldeveloped 5 month old girl weighing 10 pounds, 9 ounces (4,791 Gm.) with numerous small and large cutaneous and subcutaneous tumor nodules over her entire body. The right side of the chest was flat to percussion, and the breath sounds were markedly diminished. The left side of the chest showed compensatory emphysema.

The hemogram on this admission revealed 3,000,000 erythrocytes, 10.5 Gm. of hemoglobin and 6,800 leukocytes, with 53 per cent polymorphonuclear cells, 37 per cent lymphocytes and 10 per cent monocytes. The white cell count later rose to 15,000 with an essentially similar differential count. A roentgen metastatic series showed enlarged hilar glands, hydrothorax on the right, metastatic tumor of the right lung and pleura, metastatic tumor of the left ileum, mediastinal hernia and an enlarged liver.

June 25 and 26, 150 cc. and 200 cc., respectively, of straw-colored fluid were withdrawn from the right side of the chest. This fluid contained large mononuclear cells suggestive of a neoplastic origin. The infant gradually became

10. Herbut, P. A.; Miller, F. R., and Erf, L. A.: Am. J. Path. **21**:233, 1945.

weaker and began to refuse her feedings. She was given multiple transfusions and symptomatic therapy. She died August 7.

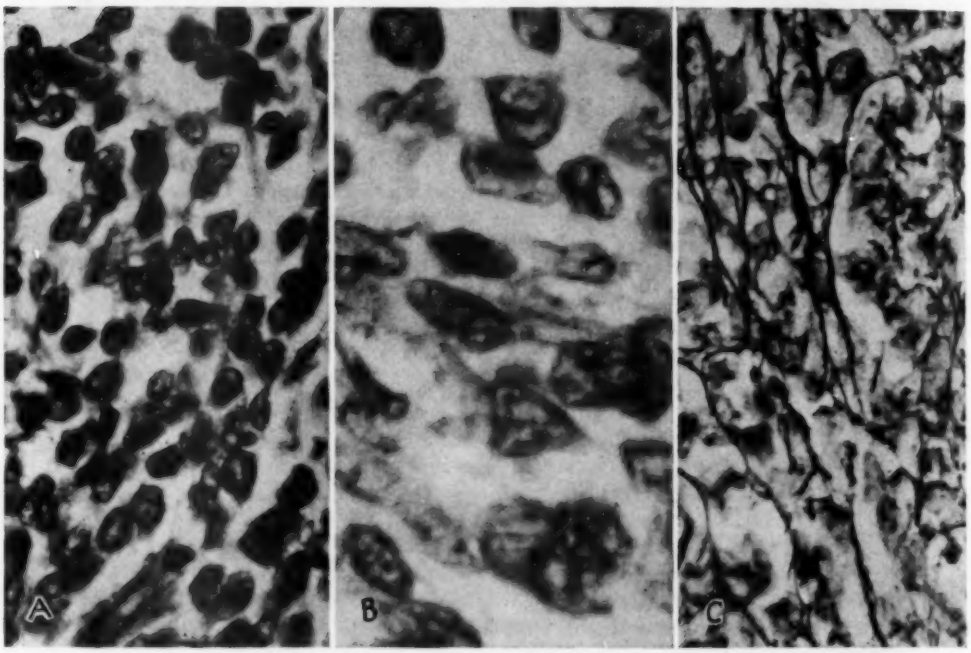
Autopsy.—The body was that of a 5 month old white girl weighing 10 pounds 8 ounces (4,762.5 Gm.) and measuring 63 cm. from vertex to heel. There were generalized pallor and moderate lividity of the thorax, the left side of the face, the skull and the dorsum of the trunk. Rigor mortis was not present. The child was greatly emaciated and cachectic. The striking objective finding was the presence of numerous cutaneous and subcutaneous nodules over the entire body. The distribution of the larger masses coincided in the main with that of lymph nodes. The cutaneous nodes were in general the smaller ones and were clearly demarcated from the surrounding tissue. They were firm, smooth and yellow, had an approximate diameter of 1 cm. and were elevated approximately 0.2 cm. above the surface of the skin. The larger nodes were not attached to the skin, nor did they cause any discoloration of it; they were only slightly movable, were moderately firm and were composed of many matted enlarged glands. The main distribution of these matted large glands was confined to the axillary and the inguinal areas. However, both large and small masses of tumor tissue were present over the left side of the head, the left temporal area, the right cheek, both axillas, both arms and forearms, the abdomen, the chest, the dorsum of the trunk, both heels and both soles. The palms were apparently the only localized area not grossly affected by the neoplastic process. The largest of these nodular protuberances was present over the manubrium. It measured 7 cm. in width, 4 cm. in length and 2 cm. in depth. It was immobile and extended into the skin in a small portion of its involved area.

The viscera revealed diffuse neoplastic infiltration. A small, pale yellow nodule was present on the anterior surface of the left ventricle, and microscopic examination revealed that this was composed of the typical young lymphoid tumor cells. The right thoracic cavity was practically entirely replaced by tumor tissue, which involved the wall, the mediastinum, the diaphragm and the small remaining portion of the right lung. The thymus could not be identified as such but rather was part of the large tumor mass extending from the superior mediastinum through the manubrium and forming a large subcutaneous mass over the upper medial area of the chest. The pancreas was also involved with tumor tissue, having an enlarged, irregular, light yellowish white nodule. The adrenal gland was free grossly of any tumor tissue, but on microscopic examination a small discrete tumor nodule was seen occupying a small portion of the cortex and medulla. A small, light yellow subcapsular nodule was present on the surface of the left kidney. There was generalized lymphadenopathy involving primarily cervical, axillary, mediastinal, mesenteric and inguinal glands. The glands had lost their usual configuration and consisted almost entirely of tumor tissue. They were pale yellow, moderately firm and matted. The gross examination of the remaining viscera revealed nothing remarkable. The tumor tissue present in the various organs was of the same morphologic character.

Microscopically, the tumor cells were young lymphoid stem cells and were approximately three to four times the size of the normal adult lymphocyte. The cytoplasm was pale staining, and the cell membrane was not sharply defined. The greater portion of the individual cell, 75 per cent, consisted of the large basophilic lymphoid nucleus, the nuclear membrane of which was sharply defined and stood out above the paler-staining nucleoplasm. Within the nucleus there was an abundance of fine chromatin tissue and a small, clearly demarcated nucleolus. Extending from the cellular membrane and connecting each cell to one or more

neighboring cells were fine argentophilic strands. These intercellular bridges were present throughout the tumor tissue but were more abundant in certain areas. The tumor tissue was not infiltrated by any normal lymphocytes or by inflammatory cells. Careful examination of the neoplastic nuclei revealed occasional mitotic figures. The abundance of reticulum and the intercellular bridge-like strands were seen in all the sections of tumor tissue but were most dramatically present in the specially stained preparations.

Final Diagnosis.—Lymphoma, stem cell type, involving the skin, lymph nodes, the right lung, the heart, the diaphragm, the kidneys, the adrenal glands and the pancreas.



A, tumor cells in a lymph node; hematoxylin and eosin; × 600.
B, tumor cells in a lymph node; hematoxylin and eosin; × 1,500.
C, tumor tissue showing a fine network of reticulum; Wilder's stain; × 600.

COMMENT

Gall and Mallory [7] have proposed the following classification of cancerous lymphomas:

1. Stem cell lymphoma. } Reticulum cell lymphoma.
2. Clasmatocytic lymphoma. }
3. Lymphoblastic lymphoma.
4. Lymphocytic lymphoma.
5. Hodgkin's lymphoma.
6. Hodgkin's sarcoma.
7. Follicular lymphoma.

This nomenclature has been adhered to in this laboratory. To my knowledge, the case reported here is the first publication of a congenital stem cell lymphoma.

The clinical course of the patient is remarkable in a number of respects. At the time of birth an irregular smooth, salmon pink, waxy tumor located over the manubrium and a palpable left axillary lymph node were noted. The mass over the sternum involved the skin as well as the subcutaneous tissue. Clinically the lesion of the skin was suggestive of lymphangioma, but biopsy of the skin revealed changes consistent with leukemia cutis. Gueft and Rosahn [11] reported a case of histiocytic leukemia occurring in an infant in whom leukemic infiltration of the skin was noted some ten months before it was manifest in the blood. With this observation in mind my associates and I made serial blood studies of our patient, which failed to reveal any significant abnormalities during life, nor were any observed at autopsy. Sugarbaker and Craver [6] in their series of 196 cases of so-called lymphosarcoma found involvement of the skin in 5.5 per cent. Cutaneous infiltration appeared in 16 to 26 per cent of the cases of various types of lymphoma reported by Gall and Mallory [7] with the exception of those of follicular lymphoma, in which cutaneous infiltration was rare. Neither of these two papers correlates the occasional development of leukemia with the presence of cutaneous lymphomatous involvement.

The initial response of the patient to roentgen therapy was characteristic of cancerous lymphoma. The tumor masses regressed immediately and the infant began to gain weight. The beneficial effects were transitory, and in less than two months the neoplastic process became uncontrollable. The terminal episode was characterized by severe respiratory distress, vital capacity having been markedly reduced by the tumor tissue and the resultant pleural effusion.

The etiology of lymphoma is no more clear than that of the majority of other cancers. While sarcoma and carcinoma have many characteristics in common, they differ in important respects. One of their most remarkable differences concerns the age of onset. Generally, the sarcoma occurs in the middle-aged group and the carcinoma in the older age group. However, as seen in the survey by Wells, the vast majority of congenital cancers have been classified as sarcoma, a group which no doubt includes an unknown number of cancers that might be classified as lymphoma. To date there is no adequate explanation for this prevalence of sarcoma in the fetal and the newborn. The clinically accepted concept that a tumor grows more rapidly in the young has been challenged by the studies of Nettleship,[12] who has transplanted

11. Gueft, B., and Rosahn, P. D.: Am. J. Clin. Path. **13**:516, 1943.

12. Nettleship, A.: Am. J. Path. **21**:147, 1945.

sarcomatous tissue in animals of different ages and found no correlation between the rate of growth of the tumor and the age of the animal.

SUMMARY

A case of congenital lymphoma of the stem cell type has been observed. A review of the pertinent literature indicates that this is the first such case to be published.

NOTE.—Because of the editorial policy of the ARCHIVES OF PATHOLOGY, the author's preferred designation, "malignant lymphoma," has been changed throughout to "cancerous lymphoma."

Notes and News

New Journals.—*Journal of Gerontology* and *Non-Technical Supplement* (published quarterly, at Springfield, Ill., by Charles C Thomas, publisher; the journal and the supplement are $6 a year in the United States, Canada and Latin America and $6.50 elsewhere; the supplement purchased separately is $3 in the United States, Canada and Latin America and $3.50 elsewhere). This journal and the supplement are published for the Gerontological Society, Inc. The journal will contain original articles on problems of aging in the field of natural and social sciences and the humanities, reviews and abstracts. The articles in the journal will be abstracted in nontechnical language in the supplement. The supplement will be sent to all regular subscribers of the journal, but yearly subscriptions to the supplement may be purchased separately. The editor is Robert A. Moore, 507 South Euclid Avenue, St. Louis 10.

Research in Medical Science. The United States Public Health Service announces the early appearance of this new journal—to be published by the National Institute of Health. The journal will be issued monthly, with two volumes to the year. The yearly subscription rates are: domestic, $5; foreign, $6.75. Subscriptions may be placed with the Superintendent of Documents, Washington 25, D. C. Other correspondence regarding the journal should be addressed to: Editor, *Research in Medical Science,* National Institute of Health, Bethesda 14, Md.

Books Received

TOPLEY AND WILSON'S PRINCIPLES OF BACTERIOLOGY AND IMMUNITY. Revised by G. S. Wilson, M.D., F.R.C.P., D.P.H., K.H.P., professor of bacteriology as applied to hygiene, University of London, London School of Hygiene and Tropical Medicine, director of the Public Health Laboratory Service, and A. A. Miles, M.A., F.R.C.P., professor of bacteriology, University of London, University College Hospital Medical School. Third edition. In two volumes. Pp. 2,098, with 302 illustrations. Price $12. Baltimore: Williams & Wilkins Company, 1946.

The first edition (1,300 pages) was published in 1929. In the present revision Professor Miles takes the place of Professor Topley who took no part in the work after 1941 and died in 1944. The division into four parts is maintained: general bacteriology, systemic bacteriology, infection and resistance, the application of bacteriology to medicine and hygiene. The chapter on soil microbiology has been omitted. There are two new chapters, one on antibacterial substances used in the treatment of infections (sulfonamide compounds, penicillin, streptomyocin, etc.) and one on the bacteriology of the air. Shigella and Salmonella, formerly included under Bacterium, now have each its own chapter. Chapter 30 on Salmonella covers forty-seven pages, four and a half of which are covered by references, one example of the care given to present new developments adequately. The lymphogranulomatous-psittacosis group is put in a chapter by itself. Otherwise the general form of the book is unchanged. At the end of each volume is the same index to both. References to the writings considered in the text are listed under authors' names at the end of each chapter. In most cases these lists

occupy several pages. They are helpful bibliographic guides. The illustrations, some 300, all in black and white, are simple but clear and effective. There are several electron micrographs. The bindings of the volumes seem much too flimsy to withstand the handling they will receive in libraries and laboratories. Part 4 presents in detail the etiology, the morbid anatomy, the epidemiology, the diagnosis, the immunology, the prevention and the treatment of human and animal diseases caused by bacteria and filtrable animal viruses. Obviously, protozoan infections are not considered. Malaria is not even mentioned in the index. This part also has chapters on the normal flora of the human body, on the bacteriology of the air, on the bacteriology of water, shell fish and sewage, and on the bacteriology of milk. The revisers apologize for the increased length of the new edition. "The war has not been conducive to careful leisurely recapitulation, and our plea must be the paradoxical excuse that we have not had time to be more concise." It is hoped that the gap due to the war's interruption of the inflow of periodicals, European and Japanese, can be filled in future editions. All parts of the revision keep well up to the high standards of the previous editions in analytic summarizing of advances on a historical background. Of course avoidable omissions and questionable propositions occur. The American work on poliomyelitis is incompletely reviewed. The congenital deformities occurring in the offspring of mothers who had rubella in the early months of pregnancy have missed mention. The difference between the scarlatinal and the erysipelatoid streptococcus toxins is still not brought out clearly enough. The inclusion of pneumococcus as Streptococcus pneumoniae as a genus under the type species of Streptococcus pyogenes will excite new interest in bacteriologic classifications. The book continues to be an at present unequaled source of explanatory information about pathogenic bacteriology. It is a cyclopedia of facts as well as a discourse on principles.

Spezielle chirurgische Therapie für Studierende und Aerzte. Bearbeitet von Dr. Max Saegesser, Privat-dozent für Chirurgie, Bern. Pp. 884, illustrated. Price, Swiss francs 80. Bern, Switzerland: Medizinischer Verlag Hans Huber, 1946.

Electrocardiography in Practice. By Captain Ashton Graybiel, M.D., United States Naval Reserve Co-Ordinator of Research, United States Naval School of Aviation Medicine, Pensacola, Florida; and Paul D. White, M.D., lecturer in medicine, Harvard Medical School; physician, Massachusetts General Hospital; with the assistance of Louise Wheeler, A.M., executive secretary, Cardiac Laboratory, Massachusetts General Hospital; and Conger Williams, M.D., assistant in medicine, Harvard Medical School and Massachusetts General Hospital. Second edition. Pp. 458, with 323 illustrations. Price $7. Philadelphia and London: W. B. Saunders Company, 1946.

Studies in Hypertony and the Prevention of Disease. By I. Harris, M.D., honorary director, Institute for Prevention of Disease, and honorary physician, Liverpool Heart Hospital, in cooperation with J. T. Ireland, G. V. James, Edward Cronin Lowe and C. E. Vernon. Pp. 114. Price $3. Baltimore: Williams & Wilkins Company, 1946.

An Experimental Study of Rationing. By R. A. McCance and E. M. Widdowson. Medical Research Council Special Report Series no. 254. Pp. 61. Price, 30 cents. London: His Majesty's Stationery Office, 1946.

The Modern Attack on Tuberculosis. By Henry D. Chadwick, M.D., and Alton S. Pope, M.D. Revised edition. Pp. 134. Price $1. New York: The Commonwealth Fund, 1946.